PATENT
Atty. Docket No.: 3804.0055

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No. 4,668,669 )
)
Issued: May 26, 1987 )
)
To: Jean-Claude Barriere, Claude Cotrel, )
Jean-Marc Paris )
)
Assignee: Rhone-Poulenc Rorer S.A. )
)
For: PRISTINAMYCIN $II_B$ DERIVATIVES )
AND COMPOSITIONS CONTAINING )
THEM )



**ATTN: BOX PATENT EXT.**
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

**APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156**

Your Applicant, Rhone-Poulenc Rorer S.A., represents that it is the Assignee of the entire interest in and to Letters Patent of the United States 4,668,669 granted to Jean-Claude Barriere, Claude Cotrel, and Jean-Marc Paris on the 26th day of May, 1987, for PRISTINAMYCIN $II_B$ DERIVATIVES AND COMPOSITIONS CONTAINING THEM, by virtue of an assignment in favor of Rhone-Poulenc Rorer S.A. The assignment to Rhone-Poulenc Sante was recorded on Reel 4504, at Frame 063, on January 10, 1986, and the name change to Rhone-Poulenc Rorer S.A. was submitted to the Patent and Trademark Office for recordation on October 5, 1999. (Attachment A)

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& DUNNER, L.L.P.
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202-408-4000

By the Power of Attorney enclosed herein (Attachment B), Applicant appoints attorneys in Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P., including Charles E. Van Horn, as attorney for Rhone-Poulenc Rorer S.A. with regard to this application for extension of the term of U.S. Patent 4,668,669 and to transact all business in the U.S. Patent and Trademark Office in connection therewith.

Applicant hereby submits this application for extension of the patent term under 35 U.S.C. § 156 by providing the following information required by the rules promulgated by the U.S. Patent and Trademark Office (37 C.F.R. § 1.740). For the convenience of the Patent and Trademark Office, the information contained in this application is presented in a format that follows the requirements of Section 1.740 of Title 37 of the Code of Federal Regulations.

(1) The approved product SYNERCID® is an association of 2 semisynthetic pristinamycin derivatives in a weight ratio of 30/70. The chemical names for the 2 semisynthetic pristinamycin derivatives are 5δR-[(3S)-3-quinuclidinyl]thiomethyl pristinamycin $I_A$ (quinupristin) and 26R-[(2-diethylaminoethyl)sulfonyl]pristinamycin $II_B$ (dalfopristin). The formulation including SYNERCID® is available in a sterile non-pyrogen freeze dried preparation which contains quinupristin and dalfopristin as their methane sulfonic salts.

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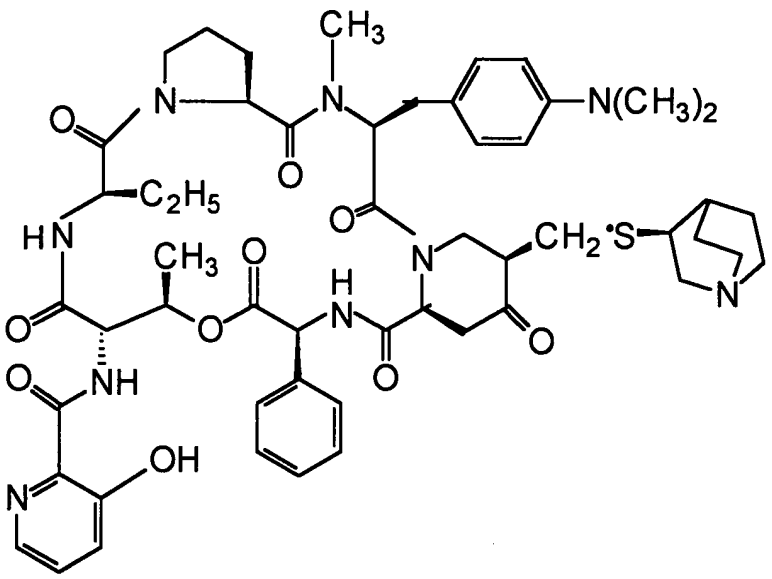
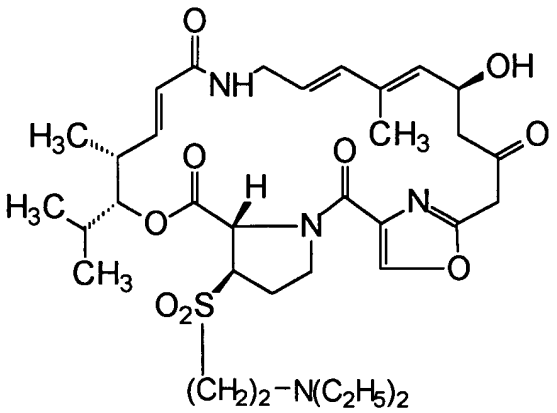
Quinupristin has the structural formula:



Dalfopristin has the structural formula:



(2) The approved product was subject to regulatory review under the Federal Food, Drug and Cosmetic Act Section 505.

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(3) The approved product SYNERCID® received permission for commercial marketing or use under Section 505 of the Federal Food, Drug and Cosmetic Act on September 21, 1999.

(4) The active ingredients in SYNERCID® are the methane sulfonate salts of 5δR-[(3S)-3-quinuclidinyl]thiomethyl pristinamycin $I_A$ (quinupristin) and 26R-[(2-diethylaminoethyl)sulfonyl]pristinamycin $II_B$ (dalfopristin), which, on information and belief, have not been approved for commercial marketing or use under Section 505 of the Federal Food, Drug and Cosmetic Act prior to the approval of NDA 50-747 for SYNERCID® by the Food and Drug Administration on September 21, 1999. A copy of the insert describing the approved product is attached (Attachment C).

(5) This application for extension of patent term under 35 U.S.C. § 156 is being submitted within the permitted 60-day period pursuant to 37 C.F.R. § 1.720(f), said period will expire on November 19, 1999.

(6) The complete identification of the patent for which a term extension is being sought is as follows:

Inventors: Jean-Claude Barriere, Claude Cotrel and Jean-Marc Paris

Patent No.: 4,668,669

Issue Date: May 26, 1987

Expiration Date: January 10, 2006 (by virtue of the patent term resetting provisions of 35 U.S.C. § 154(c)(1) enacted under the URAA).



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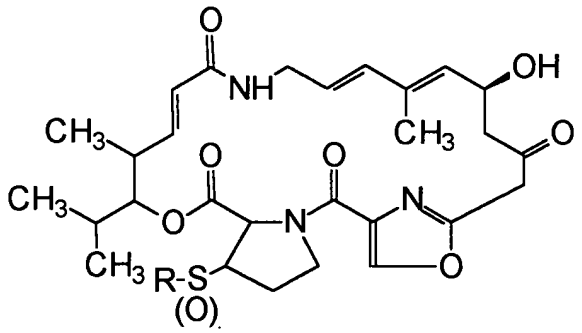
(7) A true copy of the patent is attached (Attachment D).

(8) No terminal disclaimer or reexamination certificate has been issued on this patent. A request for a certificate of correction as filed on November 2, 1999, is attached (Attachment E). A copy of the maintenance fee statement indicating payment of maintenance fees in 1990, 1994 and 1998 is attached (Attachment F).

(9) U.S. Patent 4,668,669 claims an active ingredient in the approved product in at least claims 1, 2, 5 (as corrected), and 9, and a method of using an active ingredient in claim 10. Claims 1, 2, 5 (as corrected), 9 and 10 claim at least one active ingredient in SYNERCID® as follows:

1. A pristinanycin $II_B$ of the formula:




in which R denotes

either a 3-azetidinyl, 3-pyrrolidinyl, 3- or 4-piperidinyl or 3- or 4-azepinyl radical each of which is unsubstituted or substituted by alkyl,

or alkyl of 2 to 4 carbon atoms substituted by 1 or 2 radicals chosen from phenyl, cycloalkylamino of 3 to 6 ring atoms, N-alkyl-N-cycloalkylamino of 3 to 6 ring atoms,

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alkylamino, dialkylamino, and dialkylcarbamoyloxy, the alkyl moieties of the said dialkylamino and dialkylcarbamoyloxy radicals being unjoined or joined to form, with the nitrogen atom to which they are attached, and, if required, an oxygen, sulphur, or other nitrogen atom, a 1-azetidinyl, 1-pyrrolidinyl, piperidino, 1-azepinyl, morpholino, thiomorpholino in the form of sulphoxide or sulphone, 1-piperazinyl, 4-alkyl-1-piperazinyl, N-alkyl-1-homopiperazinyl or imidazolyl radical, all of which may be unsubstituted or substituted by alkyl, or R denotes an alkyl of 2 to 4 carbon atoms substituted by 2- or 3-azetidinyl, 2- or 3-pyrroliidinyl, 2-, 3- or 4-piperidyl, 2- 3- or 4-azepinyl, piperazinyl, 4-alkyl-piperazinyl, quinolyl, isoquinolyl, or imidazolyl radical, each of which is unsubstituted or substituted by alkyl, these heterocyclic rings being linked to the alkyl of 2 to 4 carbon atoms by a carbon atom of the ring, n is 1 or 2 and, unless stated otherwise, the abovementioned alkyl radicals are linear or branched and contain 1 to 10 carbon atoms each, in its isomeric forms or their mixtures, or a pharmaceutically acceptable acid addition salt thereof.

Claim 1 reads on an active ingredient in SYNERCID®, specifically the pharmaceutically acceptable methane sulfonate salt of dalfopristin, when R is an alkyl of 2 carbon atoms substituted by dialkylamino.

2. A pristinamycin $II_B$ according to claim 1, wherein R denotes alkyl of 2 to 4 carbon atoms substituted by 1 or 2 radicals chosen from phenyl, cycloalkylamino of 5 or 6 ring atoms, N-alkyl-N-cycloalkylamino of 5 or 6 ring atoms, alkylamino of 1 to 4 carbon atoms, or dialkylamino in which each alkyl is of 1 to 3 carbon atoms or the



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alkyls form, with the nitrogen atom to which they are attached, a 1-azetidinyl, 1-pyrrolidinyl, piperidino, or 1-azepinyl radical, or R denotes a 3-azetidinyl, 3-pyrrolidinyl, 3- or 4-piperidyl or 3- or 4-azepinyl radical each of which is unsubstituted or substituted by alkyl of 1 to 4 carbon atoms, at least one of the substituents carried by the said alkyl being in a 1- or a 2-position, in its isomeric forms and their mixtures, or a pharmaceutically acceptable acid addition salt thereof.

Claim 2 likewise is directed to an active ingredient in SYNERCID®, specifically the pharmaceutically acceptable methane sulfonate salt of dalfopristin, when R is an alkyl of 2 carbons substituted by dialkylamino where each alkyl has two carbon atoms.

5. A pristinamycin $II_B$ according to claim 1 which is 26-(2-diethylaminoethyl)sulphonylpristinamycin $II_B$, its isomeric forms and their mixtures, or a pharmaceutically acceptable acid addition salt thereof.

Claim 5 (as corrected by the request for certificate of correction) is directed to an active ingredient in SYNERCID®, specifically the pharmaceutically acceptable methane sulfonate salt of dalfopristin.

9. A pharmaceutical composition comprising an effective amount of a pristinamycin $II_B$ according to claim 1 in association with a compatible pharmaceutically acceptable carrier and/or adjuvant.

Claim 9 reads on an active ingredient SYNERCID® since the active ingredient methane sulfonic salt of dalfopristin is a pharmaceutically acceptable acid additive salt of a pristinamycin $II_B$ according to claim 1.



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10. Method of controlling bacterial growth which comprises exposing said bacteria to the effect of a pristinamycin $II_B$ according to claim 1 in sufficient concentration to control said bacteria.

Claim 10 reads on a method of using an active ingredient in SYNERCID® since it reads on exposing bacteria to the effect of a pharmaceutically acceptable acid additive salt of a pristinomycin $II_B$ according to claim 1, which covers the active ingredient methane sulfonic salt of dalfopristin.

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(10) The relevant dates and information pursuant to 35 U.S.C. § 156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

Investigational New Drug Application (IND 45304) for SYNERCID® was filed May 24, 1994, and became effective on June 23, 1994, 30 days after the date of submission on May 24, 1994.

New Drug Application for SYNERCID® (NDA 50-747) was submitted on September 5, 1997.

New Drug Application for SYNERCID® was approved on September 21, 1999

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(11) A brief description of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to SYNERCID® and the dates applicable to these significant activities are set forth in a chronology of events in Attachment G.

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(12)(i) Applicant is of the opinion that U.S. Patent 4,668,669 is eligible for extension of the patent term under 35 U.S.C. § 156 because it satisfies all requirements for such extension as follows:

(a) 35 U.S.C. § 156(a) - U.S. Patent 4,668,669 claims the product SYNERCID®.

(b) 35 U.S.C. § 156(a)(1) - U.S. Patent 4,668,669 has not expired before submission of this application.

(c) 35 U.S.C. § 156(a)(2) - The term of U.S. Patent 4,668,669 has never been extended under 35 U.S.C. § 156(e)(1).

(d) 35 U.S.C. § 156(a)(3) - The application for extension is submitted by the owner of record of the patent in accordance with the requirements of paragraphs (1) through (4) of 35 U.S.C. § 156(d) and the rules of the Patent and Trademark Office.

(e) 35 U.S.C. § 156(a)(4) - The product SYNERCID® has been subjected to a regulatory review period before its commercial marketing or use.

(f) 35 U.S.C. § 156(a)(5)(A) - The commercial marketing or use of the product SYNERCID® after the regulatory review period is the first permitted commercial marketing or use under the provision of the Federal Food, Drug and Cosmetic Act (i.e., Section 505) under which such regulatory review period occurred.

(g) 35 U.S.C. § 156(c)(4) - No other patent has been extended for the same regulatory review period for the product SYNERCID®.

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(12)(ii) The length of the extension of patent term of U.S. Patent 4,668,669 claimed by Applicant is that period authorized by 35 U.S.C. § 156(c) which has been calculated to be 1333 days. The length of the extension was determined pursuant to 37 C.F.R. § 1.775 as follows:

(a) The regulatory review period under 35 U.S.C. § 156(g)(1)(B) began on June 23, 1994 and ended September 21, 1999, which is a total of 1918 days, which is the sum of (1) and (2) below:

(1) The period of review under 35 U.S.C. § 156(g)(1)(B)(i), the "Testing Period", began on June 23, 1994 and ended on September 5, 1997, which is 1171 days; and

(2) The period of review under 35 U.S.C. § 156(g)(1)(B)(ii), the "Approval Period", began on September 5, 1997, and ended on September 21, 1999, which is a total of 747 days.

(b) The regulatory review period upon which the period of extension is calculated is the entire regulatory review period as determined in subparagraph 12(ii)(a) above (1918 days) less:

(1) The number of days in the regulatory review period which were on or before the date on which the patent issued (May 26, 1987) which is zero (0) days; and

(2) The number of days during which applicant did not act with due diligence, which is zero (0) days; and



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(3) One-half the number of days determined in sub-paragraph (12)(ii)(a)(1) above after the patent issued (one-half of 1171 days) which is 585 days;

(c) The number of days as determined in sub-paragraph (12)(ii)(b) (1333 days) when added to the expiration date of the original term of the patent (January 10, 2006) would result in the date of September 4, 2009

(d) Fourteen (14) years when added to the date of the NDA approval (September 21, 1999) would result in the date of September 21, 2013;

(e) The earlier date as determined in sub-paragraphs (12)(ii)(c) and (12)(ii)(d) is September 4, 2009;

(f) Since U.S. Patent 4,668,669 issued after September 24, 1984, the period of extension may not exceed five years from the original expiration date of January 10, 2006. Five years when added to the original expiration date of the patent would result in the date of January 10, 2011.

(g) The earlier dates as determined by sub-paragraph (12)(ii)(e) and (12)(ii)(f) is September 4, 2009.

(13) Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

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(14) The prescribed fee for receiving and acting upon this application is attached as a check in the amount of $1,120.00. The Commissioner is authorized to charge any additional fees required by this application to Deposit Account No. 06-0916.

(15) All correspondence and inquiries may be directed to the undersigned, whose address, telephone number and fax number are as follows:

Charles E. Van Horn

Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.

1300 I Street, N.W.

Washington, D.C. 20005-3315

Phone: 202-408-4000

Fax: 202-408-4400

(16) Enclosed is a certification that the application for extension of patent term under 35 U.S.C. § 156 including its attachments and supporting papers is being submitted as one original and four (4) copies thereof (Attachment H).

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(17) The requisite declaration pursuant to 37 C.F.R. § 1.740(b) is attached (Attachment I).

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

By: Charles E. Van Horn
Charles E. Van Horn
Reg. No. 40,266

Date: November 10, 1999

Attachments:
Notification of Change of Name/Address of Assignee (Attachment A)
Power of Attorney (Attachment B)
Package Insert for SYNERCID® (Attachment C)
U.S. Patent 4,668,669 (Attachment D)
Copy of Request for Certificate of Correction (Attachment E)
Copy of Maintenance Fee Statement (Attachment F)
Chronology of Regulatory Review Period (Attachment G)
Certification of Copies of Application Papers (Attachment H)
Declaration Pursuant to 37 C.F.R. § 1.740(b) (Attachment I)

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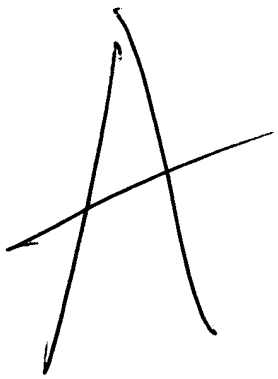


CEV

PLEASE STAMP TO ACKNOWLEDGE RECEIPT OF THE FOLLOWING:

In re U.S. Patent No. 4,668,669
Inventors: Jean-Claude Barriere et al.
Issued: May 26, 1987
Title: PRISTINAMYCIN $II_B$ DERIVATIVES AND COMPOSITIONS CONTAINING THEM

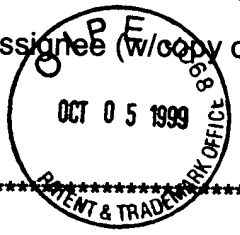
**ATTN: BOX ASSIGNMENTS**

**********

Enclosed:

1. Notification of Change of Address of Assignee (w/copy of executed translator's declaration)
2. Form PTO 1595
3. Check for $40.00

OCT 05 1999




**********

Date: 10/05/99
Case Ref.: 3804.0055
CEVanHorn/C. Woods (Drop 701)

FORM PTO-1595 (Rev. 6-93)

RECORDATION FORM COVER SHEET
PATENTS ONLY

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

Attorney Docket No. 3804.0055

To the Honorable Commissioner of Patents and Trademarks:
Please record the attached original documents or copy thereof.

ATTN. BOX ASSIGNMENTS

1. Name of conveying party(ies):

Rhône-Poulenc Sante

Additional names(s) of conveying party(ies) attached? __ Yes _X_ No

2. Name and address of receiving party(ies):

Name: Rhône-Poulenc Rorer S.A.

Internal Address: _____

Street Address: 20 avenue Raymond Aron

City: ANTONY

Cntry: France ZIP: 92160

Additional name(s) & address(es) attached?
__Yes _X No

3. Nature of conveyance:

__ Assignment __ Merger
__ Security Agreement _X_ Change of Name
__ Other _____

Execution Date: December 27, 1990

4. Application number(s) or patent number(s):
If this document is being filed together with a new application, the execution date of the application is:
_____.

A. Patent Application No.(s)

B. Patent No.(s)

4,668,669

Additional numbers attached? ___ Yes _X_ No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Internal Address: _____

Street Address: 1300 I Street, N.W.
Suite 700

City: Washington, D.C.

State: _____ ZIP: 20005-3315

6. Total number of applications and patents involved 1

7. Total fee (37 CFR 3.41): $ 40.00
_X_ Enclosed
___ Authorized to be charged to deposit account 06-0916

8. Deposit account number: 06-0916

9. Statement and signature.
To the best of my knowledge and belief, the foregoing information is true and correct, and any attached copy is a true copy of the original document.

Charles E. Van Horn, Reg. No. 40,266
Name of Person Signing

Charles E Van Horn
Signature

05 October 1999
Date

Total number of pages including cover sheet, attachments and document: 11

PATENT
Atty. Docket No. 3804.0055

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of:

Jean-Claude BARRIERE et al.

Patent No.: 4,668,669

Issued: May 26, 1987

Title: PRISTINAMYCIN $II_B$ DERIVATIVES AND COMPOSITIONS CONTAINING THEM

Assignee: Rhône-Poulenc Rorer S.A.

**ATTN: BOX ASSIGNMENTS**

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

**NOTIFICATION OF CHANGE OF NAME/ADDRESS OF ASSIGNEE**

It is requested that the records of the Patent and Trademark Office be updated to reflect the Assignee's change of name/address as follows:

RHONE-POULENC RORER S.A.
20 avenue Raymond Aron
92160 ANTONY
FRANCE

The original U.S. patent application Serial No. 817,548 (filed January 10, 1986) was assigned to RHONE-POULENC SANTE, Les Miroirs, 18 avenue d'Alsace, 92400 COURBEVOIE (France). A change of name of RHONE-POULENC SANTE to RHONE-POULENC RORER S.A. was published in The Journal Spécial des Sociétés on

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December 29, 1990. A copy of "Proces-Verbal De L'Assemblee Generale Extraordinaire" is attached, along with an executed translator's declaration. The recording fee of $40.00 (37 C.F.R. § 3.41) is enclosed.

If there are any additional fees due in connection with the filing of this Notification, please charge the fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

By: Charles E. Van Horn

Charles E. Van Horn
Reg. No. 40,266

Date: October 5, 1999

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TRANSLATOR'S DECLARATION

I, Stephen Thomas MOGER BA(Hons), translator to RWS Translations Ltd., of Europa House, Marsham Way, Gerrards Cross, Buckinghamshire, England declare:

1. That I am a citizen of the United Kingdom of Great Britain and Northern Ireland.

2. That I am well acquainted with the French and English languages.

3. That the attached is an accurate translation of the accompanying documents in the French language to the best of my knowledge and belief.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 17 June 1996

S T Moger

Stephen Thomas MOGER
For and on behalf of RWS Translations Ltd.

CERTIFIED TRUE COPY

RHONE-POULENC SANTE
Limited company with capital of F. 692,471,000
Head office: 20, avenue Raymond Aron - ANTONY (92160)
C.R.: Nanterre B 304 463 284

-=-=-=-=-=-

MINUTES
OF THE EXTRAORDINARY GENERAL MEETING
on 27th December 1990

-=-=-=-=-=-

On Thursday 27th December 1990, at 9 a.m., the shareholders of the company RHONE-POULENC SANTE met for an Extraordinary General Meeting at 25 Quai Paul DOUMER - 92408 COURBEVOIE in accordance with the letter of notification to attend which was sent to them, as well as to the auditors, on 12th December 1990.

The Meeting appointed its Board.

Mr Jean-Jacques BERTRAND, Chairman of the Board of Directors, presided over the Meeting.

Mr Hubert de FORCEVILLE, representative of the company RHONE-POULENC CHIMIE

and

Mr Marcel CHEVRIER

the two shareholders with the largest number of votes, who were present and in agreement, were appointed to serve in the capacity of Scrutineers.

Mr Yves BRISSY was appointed to serve in the capacity of

Secretary.

The Chairman stated, according to the attendance list certified accurate by the Members of the Board, that the shareholders who were present or represented owned the entirety of the shares forming the authorized capital.

The Meeting, thus bringing together more than half the authorized capital, was properly constituted and was therefore able to debate validly.

The Chairman tabled and made available to the shareholders:

1) a copy of the letter of notification to attend which was sent to each of the shareholders as well as to the Auditors,
2) the attendance list,
3) the collection of forms for voting by post or by proxy signed by the shareholders,
4) the assignment agreements,
5) the report of the Board of Directors,
6) the reports of the Auditor of the hive-off,
7) the draft resolutions,
8) the articles of association.

The Chairman then declared that the documents provided for by current legislation had been, as the case may be, either enclosed with the forms for voting by post or by proxy sent to the shareholders or made available to them within the legal time limits.

The Meeting gave him formal acknowledgement of this declaration.

The Chairman then recalled that the Meeting was called for the purpose of discussing the following agenda:

A G E N D A

- Report of the Board of Directors

- Approval of the plan for partial assignment of immovable and movable, tangible and intangible assets appertaining to the "Research and Development" branch of activity carried on at the CRVA and la Croix de Berny sites/Report of the Auditor of the hive-off.

- Approval of the plan for partial assignment of immovable and movable, tangible and intangible assets appertaining to the "Production of Active Principles" branch of activity carried on at Vitry and Villeneuve la Garenne/Report of the Auditor of the hive-off.

- Amendment of the name of the company forming the subject of article 2 of the Articles of Association of the Company.

- Powers

The Chairman then had the report of the Board of Directors read out, the text of which follows:

THIRD RESOLUTION

The General Meeting, having examined the reports of the Board of Directors, decided to modify the name of the Company which became "RHONE-POULENC RORER SA".

Consequently, article 2 of the articles of association was from then on worded as follows:

- Article 2 - Name of the Company

The name of the Company is:
RHONE-POULENC RORER SA

This resolution was carried unanimously.

CERTIFIED TRUE COPY
Chairman and Managing Director
per pro
{signature}

EXTRAIT CERTIFIE CONFORME

*RHONE-POULENC SANTE*
*Société anonyme au capital de F. 692 471 000*
*Siège social : 20, avenue Raymond Aron - ANTONY (92160)*
*R.C.S. : Nanterre B 304 463 284*

-=-=-=-=-=-

*PROCES-VERBAL*
*DE L'ASSEMBLEE GENERALE EXTRAORDINAIRE*
*du 27 Décembre 1990*

-=-=-=-=-=-

*Le Jeudi 27 Décembre 1990, à 9 heures, Messieurs les Actionnaires de la Société RHONE-POULENC SANTE se sont réunis en Assemblée Générale Extraordinaire au 25 Quai Paul DOUMER - 92408 COURBEVOIE, conformément à la lettre de convocation qui leur a été adressée, ainsi qu'aux Commissaires aux Comptes, le 12 Décembre 1990.*

*L'Assemblée procède à la composition de son bureau.*

*Monsieur Jean-Jacques BERTRAND, Président du Conseil d'Administration, préside l'Assemblée.*

*Monsieur Hubert de FORCEVILLE, représentant la Société RHONE-POULENC CHIMIE*
*et*
*Monsieur Marcel CHEVRIER*

*les deux actionnaires disposant du plus grand nombre de voix, présents et acceptant, sont appelés à remplir les fonctions de Scrutateurs.*

*Monsieur Yves BRISSY est désigné pour remplir les fonctions de Secrétaire.*

*Le Président constate, d'après la feuille de présence certifiée exacte par les Membres du bureau, que les actionnaires présents ou représentés possèdent la totalité des actions composant le capital social.*

*L'Assemblée, réunissant ainsi plus de la moitié du capital social, est régulièrement constituée et peut donc valablement délibérer.*

Le Président dépose sur le bureau et met à la disposition des actionnaires :

1°) un exemplaire de la lettre de convocation adressée à chacun des actionnai ainsi qu'aux Commissaires aux Comptes,

2°) la feuille de présence,

3°) le recueil des formulaires de vote par correspondance ou par procuration signés par les actionnaires,

4°) les traités d'apport

5°) le rapport du Conseil d'Administration,

6°) les rapports du commissaire à la scission

7°) le projet de résolutions,

8°) les statuts.

Puis, le Président déclare que les documents prévus par la législation en vigue ont été, selon le cas, soit joints aux formulaires de vote, par correspondance par procuration, adressés aux actionnaires, soit tenus à leur disposition dans les délais légaux.

L'Assemblée lui donne acte de cette délaration.

Puis, Monsieur le Président rappelle que l'Assemblée est réunie en vue de délibérer sur l'ordre du jour suivant :

O R D R E  D U  J O U R

- Rapport du Conseil d'Administration

- Approbation du projet d'apport partiel d'actif des éléments immobiliers et mobiliers, corporels et incorporels dépendant de la branche d'activité "Recherche et Développement" exploitée sur les sites du CRVA et de la Croix de Berny/Rapport du Commissaire à la scission.

- Approbation du projet d'apport partiel d'actif des éléments immobiliers et mobiliers, corporels et incorporels dépendant de la branche d'activité "Production de Principes Actifs" exploitée à Vitry et Villeneuve la Garenne/Rapport du Commissaire à la scission.

- Modification de la dénomination sociale faisant l'objet de l'article 2 des Statuts de la Société.

- Pouvoirs

Monsieur le Président fait ensuite donner lecture du rapport du Conseil d'Administration dont la [illegible]

.....

*TROISIEME RESOLUTION*

*L'Assemblée Générale, après avoir pris connaissance des rapports du Conseil d'Administration, décide de modifier la dénomination sociale de la Société qui devient "RHONE-POULENC RORER SA".*

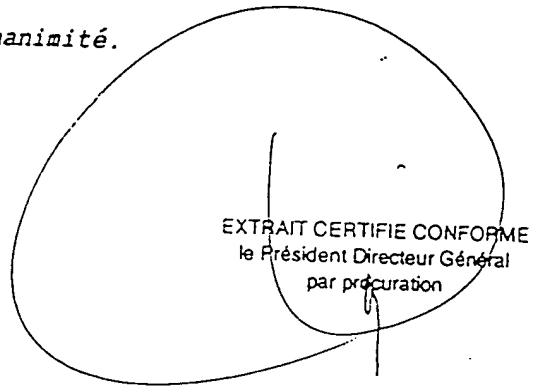
*En conséquence l'article 2 des statuts est dorénavant rédigé comme suit :*

- *Article 2 - Dénomination sociale*

*La Société a pour dénomination :*

*RHONE-POULENC RORER SA*

*Cette résolution est adoptée à l'unanimité.*



PATENT
Atty. Docket No.: 3804.0055

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No. 4,668,669 )
)
Issued: May 26, 1987 )
)
To: Jean-Claude Barriere, Claude Cotrel, )
Jean-Marc Paris )
)
Assignee: Rhone-Poulenc Rorer S.A. )
)
For: PRISTINAMYCIN $II_B$ DERIVATIVES )
AND COMPOSITIONS CONTAINING )
THEM )

**ATTN: BOX PATENT EXTENSION**
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

**POWER OF ATTORNEY**

Rhone-Poulenc Rorer S.A. is the Assignee of the entire right, title, and interest in the patent identified above by virtue of an assignment recorded in the Patent and Trademark Office at Reel 4505, at Frame 063 on January 10, 1986, and name change submitted to the Patent and Trademark Office for recordation on October 5, 1999.

Assignee, Rhone-Poulenc Rorer S.A., being the owner of the above-identified U.S. Letters Patent, hereby grants the power of attorney to **FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.**, Douglas B. Henderson, Reg. No. 20,291; Ford F. Farabow, Jr., Reg. No. 20,630; Arthur S. Garrett, Reg. No. 20,338; Donald R. Dunner, Reg. No. 19,073; Brian G. Brunsvold, Reg. No. 22,593; Tipton D. Jennings, IV, Reg. No. 20,645; Jerry D. Voight, Reg. No. 23,020; Laurence R. Hefter, Reg. No.

20,827; Kenneth E. Payne, Reg. No. 23,098; Herbert H. Mintz, Reg. No. 26,691; C. Larry O'Rourke, Reg. No. 26,014; Albert J. Santorelli, Reg. No. 22,610; Michael C. Elmer, Reg. No. 25,857; Richard H. Smith, Reg. No. 20,609; Stephen L. Peterson, Reg. No. 26,325; John M. Romary, Reg. No. 26,331; Bruce C. Zotter, Reg. No. 27,680; Dennis P. O'Reilley, Reg. No. 27,932; Allen M. Sokal, Reg. No. 26,695; Robert D. Bajefsky, Reg. No. 25,387; Richard L. Stroup, Reg. No. 28,478; David W. Hill, Reg. No. 28,220; Thomas L. Irving, Reg. No. 28,619; Charles E. Lipsey, Reg. No. 28,165; Thomas W. Winland, Reg. No. 27,605; Basil J. Lewris, Reg. No. 28,818; Martin I. Fuchs, Reg. No. 28,508; E. Robert Yoches, Reg. No. 30,120; Barry W. Graham, Reg. No. 29,924; Susan Haberman Griffen, Reg. No. 30,907; Richard B. Racine, Reg. No. 30,415; Thomas H. Jenkins, Reg. No. 30,857; Robert E. Converse, Jr., Reg. No. 27,432; Clair X. Mullen, Jr., Reg. No. 20,348; Christopher P. Foley, Reg. No. 31,354; John C. Paul, Reg. No. 30,413; Roger D. Taylor, Reg. No. 28,992; David M. Kelly, Reg. No. 30,953; Kenneth J. Meyers, Reg. No. 25,146; Carol P. Einaudi, Reg. No. 32,220; Walter Y. Boyd, Jr., Reg. No. 31,738; Steven M. Anzalone, Reg. No. 32,095; Jean B. Fordis, Reg. No. 32,984; Barbara C. McCurdy, Reg. No. 32,120; James K. Hammond, Reg. No. 31,964; Richard V. Burgujian, Reg. No. 31,744; J. Michael Jakes, Reg. No. 32,824; Thomas W. Banks, Reg. No. 32,719; Christopher P. Isaac, Reg. No. 32,616; Bryan C. Diner, Reg. No. 32,409; M. Paul Barker, Reg. No. 32,013; Andrew Chanho Sonu, Reg. No. 33,457; David S. Forman, Reg. No. 33,694; Vincent P. Kovalick, Reg. No. 32,867; James W. Edmondson, Reg. No. 33,871; Michael R. McGurk, Reg. No. 32,045; Joann M. Neth, Reg. No. 36,363; Gerson S. Panitch, Reg. No. 33,751; Cheri M.

Taylor, Reg. No. 33,216; Charles E. Van Horn, Reg. No. 40,266; Linda A. Wadler, Reg. No. 33,218; Jeffrey A. Berkowitz, Reg. No. 36,743; Michael R. Kelly, Reg. No. 33,921; and James B. Monroe, Reg. No. 33,971, both jointly and separately to be attorneys for Rhone-Poulenc Rorer S.A. with regard to an application for extension of the term of U.S. Patent 4,668,669 and to transact all business in the Patent and Trademark Office connected therewith.

The undersigned is empowered to act on behalf of the Assignee.

Please send all future correspondence concerning the above matter to Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P., at the following address:

Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.
1300 I Street, N.W.
Washington, D.C. 20005-3315

RHONE-POULENC RORER S.A.

Date: November 4, 1999

Françoise Lobjois
Name: Françoise Lobjois

Title: Executive

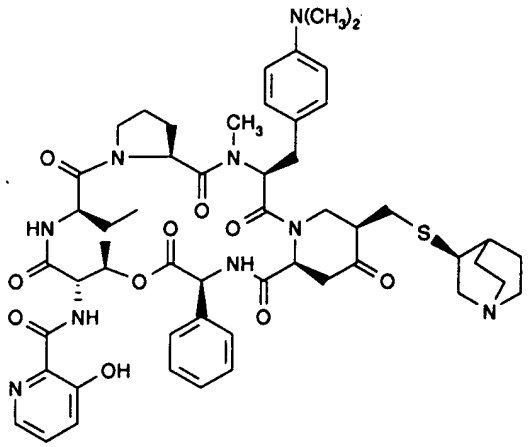
Synercid®
(quinupristin-dalfopristin) IV

## DESCRIPTION

**Synercid®** (quinupristin/dalfopristin) I.V., a streptogramin antibacterial agent for intravenous administration, is a sterile freeze-dried formulation of two semisynthetic pristinamycin derivatives, quinupristin (derived from pristinamycin I) and dalfopristin (derived from pristinamycin IIA) in the ratio of 30:70 (w/w).

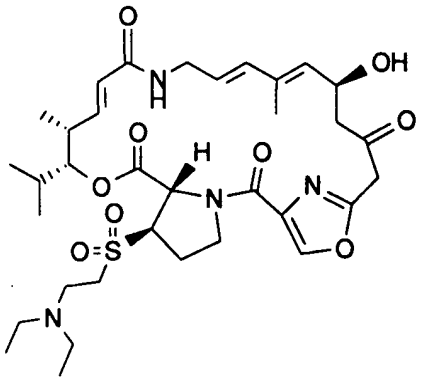
Quinupristin is a white to very slightly yellow, hygroscopic powder. It is a combination of three peptide macrolactones. The main component of quinupristin (>88.0%) has the following chemical name: N-[(6*R*,9*S*,10*R*,13*S*,15a*S*,18*R*,22*S*,24a*S*)-22-[*p*-(dimethylamino)benzyl]-6-ethyldocosahydro-10,23-dimethyl-5,8,12,15,17,21,24-heptaoxo-13-phenyl-18-[[(3*S*)-3-quinuclidinylthio]methyl]-12*H*-pyrido[2,1-*f*]pyrrolo-[2,1-*l*][1,4,7,10,13,16]-oxapentaazacyclononadecin-9-yl]-3-hydroxypicolinamide.

The main component of quinupristin has an empirical formula of $C_{53}H_{67}N_9O_{10}S$, a molecular weight of 1022.24 and the following structural formula:




Dalfopristin is a slightly yellow to yellow, hygroscopic, powder. The chemical name for dalfopristin is: (3*R*,4*R*,5*E*,10*E*,12*E*,14*S*,26*R*,26a*S*)-26-[[2-(diethylamino)ethyl]sulfonyl]-8,9,14,15,24,25,26,26a-octahydro-14-hydroxy-3-isopropyl-4,12-dimethyl-3*H*-21,18-nitrilo-1*H*,22*H*-pyrrolo[2,1-*c*][1,8,4,19]-dioxadiazacyclotetracosine-1,7,16,22(4*H*,17*H*)-tetrone.

Dalfopristin has an empirical formula of $C_{34}H_{50}N_4O_9S$, a molecular weight of 690.85 and the following structural formula:



**Synercid** is supplied as a sterile freeze-dried preparation of quinupristin and dalfopristin mesylate for injection in 500 mg single-dose vials.

## CLINICAL PHARMACOLOGY

**Pharmacokinetics:** Quinupristin and dalfopristin are the main active components circulating in plasma in human subjects. Quinupristin and dalfopristin are, however, rapidly converted to several major metabolites: two conjugated metabolites for quinupristin (one with glutathione and one with cysteine) and one non-conjugated for dalfopristin (formed by drug hydrolysis). *In vitro* synergism of quinupristin's metabolites with dalfopristin, and of dalfopristin's metabolite with quinupristin, has been demonstrated. (See **Microbiology**.)

Pharmacokinetic profiles of quinupristin and dalfopristin in combination with their metabolites were determined using bioassay following multiple 60-minute infusions of **Synercid** in two groups of healthy young male volunteers. Each group received 7.5 mg/kg intravenously q12h or q8h for a total of 9 and 10 doses, respectively. The pharmacokinetic parameters were comparable with q12h or q8h dosing; those of the q8h regimen are shown in the following table:

**Mean Steady-State Pharmacokinetic Parameters of Quinupristin and Dalfopristin in Combination with their Metabolites (± SD[1]) n=10**

| | Cmax[2] (μg/mL) | AUC[3] (μg.h/mL) | t ½[4] (hr) |
|---|---|---|---|
| **Quinupristin and metabolites** | 3.20 ± 0.67 | 7.20 ± 1.24 | 3.07 ± 0.51 |
| **Dalfopristin and metabolite** | 7.96 ± 1.30 | 10.57 ± 2.24 | 1.04 ± 0.20 |

[1] SD= Standard Deviation
[2] $C_{max}$ = Maximum drug plasma concentration
[3] AUC = Area under the drug plasma concentration-time curve
[4] $t_{1/2}$ = Half-life

The clearances of unchanged quinupristin and dalfopristin are similar (0.7 L/h/kg), and the apparent volume of distribution for both products is approximately 1.0 L/kg. The elimination half-life of quinupristin and dalfopristin is approximately 0.9 and 0.75 hours, respectively.

The protein binding ranges from 55 to 78% for quinupristin and from 11 to 26% for dalfopristin.

Penetration of unchanged quinupristin and dalfopristin in noninflammatory blister fluid corresponds to about 19% and 11% of that estimated in plasma, respectively. The penetration into blister fluid of quinupristin and dalfopristin in combination with their major metabolites was in total approximately 40% compared to that in plasma.

Radiolabeled quinupristin and dalfopristin were shown to penetrate into *ex vivo* human macrophages with ratios of intracellular to extracellular concentrations of 60:1 for quinupristin and 30:1 for dalfopristin after 1 hour. A slow release from macrophages was complete at 5 hours for both quinupristin and dalfopristin.

In a mouse model of *Streptococcus pneumoniae*, **Synercid** penetration into the lung was demonstrated.

In a rabbit model of *Streptococcus pneumoniae* meningitis, a pharmacodynamic effect of intravenous **Synercid** was demonstrated, but pharmacokinetic data were not collected.

*In vitro*, the transformation of the parent drugs into their major active metabolites occurs by non-enzymatic reactions and is not dependent on cytochrome-P450 or glutathione-transferase enzyme activities. However, **Synercid** has been shown to be an inhibitor of the CYP 3A4 isoenzyme. (See **Drug Interactions**.)

Fecal excretion constitutes the main elimination route for both parent drugs and their metabolites (75-77% of dose). Urinary excretion accounts for approximately 15% of the quinupristin and 19% of the dalfopristin dose. Preclinical data in rats have demonstrated that approximately 80% of the dose is excreted in the bile and suggest that in man, biliary excretion is probably the principal route for fecal elimination.

**Special Populations**
*Elderly:* The pharmacokinetics of quinupristin and dalfopristin are not modified in the elderly.

*Gender:* The pharmacokinetics of quinupristin and dalfopristin are not modified with gender.

*Renal Insufficiency* (Creatinine clearance 6-28 mL/min): The AUC of quinupristin and dalfopristin in combination with their major metabolites increased about 1.4- and 1.3- fold, respectively. (See **DOSAGE AND ADMINISTRATION.**)

In patients undergoing Continuous Ambulatory Peritoneal Dialysis, dialysis clearance for quinupristin, dalfopristin and their metabolites is negligible. The plasma AUC of unchanged quinupristin and dalfopristin increased about 1.2- and 1.3- fold, respectively. (See **DOSAGE AND ADMINISTRATION.**) The high molecular weight of both components of **Synercid** suggests that it is unlikely to be removed by hemodialysis.

*Hepatic Insufficiency:* In patients with hepatic cirrhosis, the terminal half-life of quinupristin and dalfopristin was not modified. However, the AUC of quinupristin and dalfopristin in combination

with their major metabolites increased about 2.8- and 1.5- fold, respectively.(See **DOSAGE AND ADMINISTRATION** and **PRECAUTIONS.**)

*Obese:* In obese patients, the Cmax and AUC of quinupristin increased about 1.3-fold and those of dalfopristin about 1.4-fold. (See **DOSAGE AND ADMINISTRATION** and **PRECAUTIONS.**)

*Pediatric Patients:* The pharmacokinetics of **Synercid** in pediatric patients have not been studied.

**Microbiology:** The streptogramin components of **Synercid**, quinupristin and dalfopristin, individually possess bacteriostatic activity against Gram-positive bacteria, as do the principal components, PI and PIIA, of the naturally occurring streptogramin, pristinamycin. The main target of quinupristin and dalfopristin is the bacterial ribosome. When combined, quinupristin and dalfopristin, as **Synercid**, exert bactericidal activity by inhibiting early and late phases of bacterial protein synthesis and interact synergistically at the ribosomal site so that **Synercid's** activity is much greater than that of the components individually. Therefore, the mode of action of streptogramins, *e.g.*, **Synercid**, differs somewhat from that of the macrolides and lincosamides.

The high affinity of **Synercid** to bind to the ribosome contributes to its bactericidal activity which is uncharacteristic of the non-streptogramin members of the Macrolide-Lincosamide-Streptogramin (MLS) antibiotics. Consequently, **Synercid** has improved activity against pathogens resistant to macrolides and lincosamides. **Synercid** is also frequently active against pathogens resistant to β-lactam, glycopeptide, and quinolone antibiotics due to differences in chemical structure and mode of action.

A prolonged post-antibiotic effect (PAE) of **Synercid** was observed with *Staphylococcus aureus* (10 hours) and *Streptococcus pneumoniae* (9.1 hours) in the neutropenic mouse thigh abscess model, confirming *in vitro* data.

*In vitro* tests with *S. aureus*, including methicillin- and erythromycin-resistant strains, often show **Synercid** to act synergistically with some β-lactam agents, especially the cephalosporins. *In vitro* tests with some strains of vancomycin-resistant *E. faecium* show **Synercid** to act synergistically with glycopeptides.

Antagonism was generally not reported for any Gram-positive pathogens. *In vitro* tests with antibiotics active against *Pseudomonas aeruginosa* or *Enterobacteriaceae*, *e.g.* cefotaxime, ciprofloxacin, aztreonam, or gentamicin, did not show antagonism with **Synercid**.

Quinupristin and dalfopristin's metabolites also contribute to the antimicrobial activity of **Synercid** because their MICs range from comparable to severalfold lower than those of either quinupristin or dalfopristin. In addition, *in vitro* synergism of the major metabolites with the complementary parent compound has been demonstrated. (See **Pharmacokinetics.**)

**Synercid** has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section.

<u>Aerobic gram-positive microorganisms</u>

*Enterococcus faecium* (including Van A {Vancomycin-resistant and Teicoplanin-resistant} and Van B {Vancomycin-resistant and Teicoplanin-susceptible} strains)
*Staphylococcus aureus* (including methicillin-resistant strains)
*Staphylococcus epidermidis* (including methicillin-resistant strains)
*Streptococcus agalactiae*
*Streptococcus pyogenes*
*Streptococcus pneumoniae* (penicillin-susceptible strains)

The following *in vitro* data are available, **but their clinical significance is unknown.**
**Synercid** exhibits *in vitro* minimal inhibitory concentrations (MICs) of $\leq 1$ μg/mL against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of **Synercid** in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

**Aerobic gram-positive microorganisms**

*Corynebacterium jeikeium*
*Listeria monocytogenes*
*Staphylococcus capitis*
*Staphylococcus haemolyticus*
*Staphylococcus hominis*
*Staphylococcus saprophyticus*
*Staphylococcus simulans*
*Staphylococcus warneri*
*Streptococcus pneumoniae* (penicillin-resistant strains)
Viridans group streptococci

**Aerobic gram-negative microorganisms**

*Legionella pneumophila*
*Legionella* spp.
*Moraxella catarrhalis*
*Neisseria gonorrhoeae* (including β-lactamase-producing strains)
*Neisseria meningitidis*

**Anaerobic microorganisms**

*Porphyromonas asaccharolytica*

**Atypical microorganisms**

*Chlamydia pneumoniae*
*Mycoplasma pneumoniae*

## SUSCEPTIBILITY TESTS

**Dilution techniques:** Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of quinupristin/dalfopristin (30:70) powder (1). The MIC values should be interpreted according to the following criteria:

For testing rapidly growing aerobic microorganisms and *S. pneumoniae*:

| MIC (µg/mL) | Interpretation |
|---|---|
| ≤ 1 | Susceptible (S) |
| 2 | Moderately Susceptible (MS) |
| ≥ 4 | Resistant (R) |

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Moderately Susceptible" indicates that the result should be considered equivocal, and if the infection cannot be treated with alternative, clinically feasible drugs, the test should be repeated. This category provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control organisms to control the technical aspects of the laboratory procedures. Standard quinupristin/dalfopristin powder should provide the following MIC values:

| Microorganism | MIC (µg/mL) |
|---|---|
| *Staphylococcus aureus* ATCC 29213 | 0.25 to 1 |
| *Streptococcus pneumoniae* ATCC 49619[a] | 0.25 to 1 |
| *Enterococcus faecalis* ATCC 29212 | 2 to 8 |

[a] This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a broth microdilution procedure using cation-adjusted Mueller-Hinton broth with 2-5% lysed (freeze thaw method) horse blood (1).

**Diffusion techniques:** Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure requires the use of standardized inoculum concentrations (2). This procedure uses paper disks impregnated with 15 µg quinupristin/dalfopristin (30:70) to test the susceptibility of microorganisms to **Synercid**.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 15 µg quinupristin/dalfopristin disk should be interpreted according to the following criteria:

For testing rapidly growing aerobic microorganisms and *S. pneumoniae*:

| Zone Diameter (mm) | Interpretation |
|---|---|
| ≥ 19 | Susceptible (S) |
| 16-18 | Moderately Susceptible (MS) |
| ≤ 15 | Resistant (R) |

Interpretation should be stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for quinupristin/dalfopristin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control organisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 15-μg quinupristin/dalfopristin disk should provide the following zone diameters in these laboratory test quality control strains:

| Microorganism | Zone Diameter (mm) |
|---|---|
| *Staphylococcus aureus* ATCC 25923 | 23-29 |
| *Streptococcus pneumoniae* ATCC 49619[a] | 19-24 |

[a] This quality control range is applicable to only *S. pneumoniae* ATCC 49619 using Mueller-Hinton agar supplemented with 5% whole sheep blood incubated in 5% $CO_2$.

## INDICATIONS AND USAGE

**Synercid** is indicated in adults for the treatment of the following infections when caused by susceptible strains of the designated microorganisms, for which intravenous therapy is appropriate.

**Synercid** should be used in combination with appropriate anti-Gram-negative antibiotics if culture-proven or suspected pathogens are Gram-negative.

**Complicated skin and skin structure infections** caused by *Staphylococcus aureus* (including methicillin-resistant strains), *Staphylococcus epidermidis* (including methicillin-resistant strains), *Streptococcus agalactiae*, and *Streptococcus pyogenes*, including cases associated with concurrent bacteremia with these microorganisms.

**Nosocomial pneumonia** caused by *Staphylococcus aureus* (including methicillin-resistant strains) and *Streptococcus pneumoniae*, including cases associated with concurrent bacteremia with these microorganisms.

**Community-acquired pneumonia** caused by culture-proven monomicrobic *Streptococcus pneumoniae*, including cases associated with concurrent bacteremia.

**Infections due to Vancomycin-resistant *Enterococcus faecium* (VREF)**, including cases associated with concurrent bacteremia.

**Infections caused by *Staphylococcus aureus*** (including methicillin-susceptible and methicillin-resistant strains), in patients failing other therapies, including cases associated with concurrent bacteremia.

**Synercid** was used successfully in a limited number of pediatric patients in non-comparative clinical studies.

**Synercid** can be used for treatment of the above indications in beta-lactam-, quinolone- or glycopeptide-allergic or -intolerant patients.

## CONTRAINDICATIONS

**Synercid** is contraindicated in patients with known hypersensitivity to **Synercid** or with prior hypersensitivity to other streptogramins (*e.g.* pristinamycin or virginiamycin).

## WARNINGS

**Synercid** infusion should not be administered as an intravenous bolus.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including **Synercid**, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis". After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

## PRECAUTIONS

**General**: Following completion of the infusion, the vein should be flushed with 5% Dextrose solution to minimize venous irritation. It is recommended not to flush with saline or heparin immediately after **Synercid** administration.

If moderate to severe venous irritation occurs following peripheral administration of **Synercid**, consideration should be given to increasing the infusion volume to 500 or 750 mL, changing the infusion site, or infusing by a peripherally inserted central catheter (PICC) or a central venous catheter.

The safety and efficacy of an intravenous infusion duration other than 60 minutes have not been studied.

Episodes of arthralgia and myalgia, some severe, have been reported primarily in patients treated with a q8h regimen. In case severe or protracted arthralgia and myalgia occur, a switch to a q12h regimen may be considered.

Data from clinical trials of **Synercid** suggest that the incidence of adverse effects in patients with chronic liver insufficiency or cirrhosis was comparable to that in patients with normal hepatic function. Based on the pharmacokinetic parameters in patients with hepatic cirrhosis, a dosage reduction to 5 mg/kg of **Synercid** is recommended if the tolerability of **Synercid** at the dose of 7.5 mg/kg is not acceptable. (See **Pharmacokinetics** and **DOSAGE AND ADMINISTRATION.**)

As with other antimicrobials, use of **Synercid** may result in overgrowth of non-susceptible microorganisms. Repeated evaluation of the patient's condition is essential. Should superinfection occur during therapy, appropriate measures should be taken.

**Drug Interactions**: *In vitro* drug interaction studies have demonstrated that only CYP 3A4 is significantly inhibited by **Synercid**. In *in vitro* studies, **Synercid** inhibited the CYP 3A4 metabolism of cyclosporin A, midazolam, nifedipine and terfenadine. Thus, it is reasonable to expect that the concomitant administration of **Synercid** and other drugs primarily metabolized by the cytochrome P450 3A4 enzyme system may result in plasma levels of these drugs that could prolong their therapeutic effect and/or increase adverse reactions. Therefore, dosage adjustment of these agents may be necessary. Concomitant administration of a single dose of cyclosporin A and **Synercid** in healthy volunteers led to elevated plasma levels of cyclosporin A. Therefore, a dosage reduction of cyclosporin A based on monitoring of cyclosporin A levels may be necessary.

*In vitro* drug interaction studies have shown that **Synercid** does not significantly inhibit human CYP 1A2, 2A6, 2C9, 2C19, 2D6, or 2E1. Therefore, clinical interactions with drugs metabolized by these P450 isoenzymes are not expected.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term carcinogenicity studies in animals have not been conducted with **Synercid**. Genetic toxicity studies were performed with **Synercid**, in bacterial *in vitro* and in both *in vivo* and *in vitro* mammalian tests. The tests used included the bacterial reverse mutation (Ames test), the CHO/HGPRT gene mutation test, the *in vitro* unscheduled DNA synthesis test in rat hepatocytes, the chromosome aberration test in CHO-K1 cells and the *in vivo* mouse micronucleus test in bone marrow. No evidence for *in vitro* mutagenic activity and no induction of DNA repair or *in vivo* clastogenic effect of **Synercid**, dalfopristin or quinupristin were detected with these tests. **Synercid** was negative in the *in vitro* chromosome aberration test in CHO-K1 cells. When tested individually, a positive response was observed with dalfopristin at highly cytotoxic concentrations. A negative response was observed with quinupristin.

No impairment of fertility or peri/post natal development was observed in rats.

**Pregnancy:Teratogenic Effects**: Pregnancy Category C: No teratogenic effect was evidenced in embryofetal toxicity studies performed in rats and mice with intravenous doses of **Synercid** up to 120 mg/kg/day (corresponding to approximately 5 times in rats and 2 times in mice the human daily recommended dose). Slight fetal immaturity was observed at 120 mg/kg/day and at 40 mg/kg/day in rats and mice, respectively. In rabbits, as expected from its antibacterial activity, the administration of **Synercid** from 2 to 120 mg/kg/day (corresponding to approximately 10 times lower to 5 times higher than the human daily recommended dose) produced gastrointestinal disturbances resulting in high maternal toxicity. This did not allow for the meaningful assessment of the relationship between **Synercid** and embryofetal development. However, no increased incidence of fetal malformations was noted.

There are, however, no adequate and well-controlled studies with **Synercid** in pregnant women. Because animal reproduction studies are not always predictive of the human response, **Synercid** should be used during pregnancy only if clearly needed.

**Nursing mothers**: In lactating rats, quinupristin was excreted in milk. It is not known whether **Synercid** is excreted in human breast milk. Consequently, **Synercid** should not be administered to a breast-feeding woman.

The following systemic adverse reactions were reported: arthralgia (9.5%), myalgia (7.3%), and asthenia (1.1%).

Adverse reactions reported with an incidence of less than 1% but greater than 0.1% included hyponatremia, anorexia, hypotension, back pain, cyclosporin level increased, tachycardia, jaundice, hepatitis and pharyngitis.

No cases of ototoxicity or Red Man Syndrome were reported in clinical trials with **Synercid**.

The clinical profile of **Synercid** suggests there is no nephrotoxic effect.

In these clinical trials, death was reported as possibly related to **Synercid** in 0.3% of patients.

**Laboratory Changes:** In the comparative clinical trials, increases in total and conjugated bilirubin greater than 5 times the ULN (Upper Limit of Normal) were reported in 0.9% and 3.1% of patients, respectively.

Other laboratory changes reported as clinically significant, irrespective of the relationship to **Synercid** administration, are listed below:

| LABORATORY CHANGES | |
|---|---|
| Incidence greater than 1% | ***increases*** in eosinophils, blood urea nitrogen, gammaglutamyl transferase, lactate dehydrogenase, creatinine phosphokinase, AST, ALT, blood glucose, alkaline phosphatase, creatinine.<br><br>***decreases*** in hemoglobin, hematocrit.<br><br>***increases and decreases*** in potassium, platelets. |

One case of severe thrombocytopenia was reported.

In addition in the non-comparative clinical trials, the discontinuation rate due to adverse laboratory reactions possibly or probably related to **Synercid** was 2.0%. Most patients discontinued because of liver function test abnormalities.

Decrease in white blood cells, carbon dioxide, neutrophils, and bicarbonate were reported, also with an incidence greater than 1%. One case of pancytopenia was reported.

## OVERDOSAGE

No cases of overdose with **Synercid** have been reported. Patients who receive an overdose should be carefully observed and given supportive treatment. Synercid is not removed by peritoneal dialysis. (See **Pharmacokinetics**.) The high molecular weight of both components of **Synercid** suggests that it is unlikely to be removed by hemodialysis.

**Pediatric use**: The safety and efficacy of **Synercid** in pediatric patients was evaluated in a limited number of patients under emergency conditions at a dose of 7.5 mg/kg. (See **INDICATIONS** and **DOSAGE AND ADMINISTRATION.**)

## ADVERSE REACTIONS

The safety of **Synercid** was evaluated in 1099 patients enrolled in 5 comparative clinical trials (2 for Complicated skin and skin structure infections, 1 for Nosocomial pneumonia, and 2 for Community-acquired pneumonia). Additionally, 4 non-comparative clinical trials were conducted in 1199 patients who received **Synercid** for infections due to Gram-positive pathogens for which no other treatment option was appropriate. In this population, the patients were severely ill, with multiple background diseases, physiological impairments, and intolerant to other antibacterial therapies.

In the comparative clinical trials, the discontinuation rate due to adverse reactions possibly or probably related to **Synercid** was 6.1% for systemic reactions and 10.7% for local reactions, respectively. For the systemic adverse reactions, most patients discontinued due to rash (1%), nausea (0.8%), vomiting (0.5%), pruritus (0.5%), and pain (0.5%).

Adverse reactions possibly or probably related to **Synercid** administration are listed below:

| ADVERSE REACTIONS | |
|---|---|
| Incidence equal to or greater than 1% | **Local adverse reactions:** inflammation (42%), pain (40%), edema (17.3%), infusion site reaction (13.4%), thrombophlebitis (2.4%) **Systemic adverse reactions:** nausea (4.6%), diarrhea (2.7%), vomiting (2.7%) rash (2.5%), headache (1.6%), pruritus (1.5%), pain (1.5%). |

Additional adverse reactions that were possibly or probably related to **Synercid** with an incidence less than 1% but greater than 0.1% within each body system are listed below:

**Body as a whole:** abdominal pain, aggravation reaction, allergic reaction, cellulitis, chest pain, fever, infection;
**Cardiovascular:** palpitation, phlebitis;
**Digestive:** constipation, dyspepsia, oral moniliasis, pancreatitis, pseudomembranous enterocolitis, stomatitis;
**Metabolic:** gout, peripheral edema;
**Musculoskeletal:** arthralgia, myalgia, myasthenia;
**Nervous:** anxiety, confusion, dizziness, hypertonia, insomnia, leg cramps, paresthesia, vasodilatation;
**Respiratory:** dyspnea, pleural effusion, pneumonia;
**Skin and appendages:** maculopapular rash, sweating, urticaria;
**Urogenital:** hematuria, urinary tract infection, vaginitis;

In addition, in the non-comparative trials, the discontinuation rate due to systemic and local adverse reactions was 5.4%and 0.7%, respectively. Most patients discontinued because of arthralgia (2.3%) and myalgia (1.8%).

## DOSAGE AND ADMINISTRATION

The recommended dose of **Synercid** in adults is 7.5 mg/kg of actual body weight administered by intravenous administration (See **WARNINGS**) in 5% Dextrose solution over a 60-minute period, q8 hours or q12 hours. An infusion pump may be used to control the rate of infusion.

| INDICATIONS* | Dose (mg/kg) | Frequency | Recommended Treatment Duration (days) |
|---|---|---|---|
| Complicated skin and skin structure infections | 7.5 | q12h | 7 |
| Community-acquired pneumonia caused by monomicrobic *Streptococcus pneumoniae* | 7.5 | q12h | 7 |
| Nosocomial pneumonia | 7.5 | q8h | 10 |
| Infections caused by Vancomycin-resistant *Enterococcus faecium* | 7.5 | q8h | ** |
| Infections caused by *Staphylococcus aureus* (including methicillin-susceptible and methicillin-resistant strains) | 7.5 | q8h | ** |

*** including cases associated with concurrent bacteremia**
****depends on site and severity of infection**

**Special Populations**
*Elderly:* No dosage adjustment of **Synercid** is required for use in the elderly. (See **Pharmacokinetics**.)

*Renal insufficiency:* No dosage adjustment of **Synercid** is required for use in renally impaired patients and patients undergoing peritoneal dialysis. (See **Pharmacokinetics**.)

*Hepatic insufficiency:* Data from clinical trials of **Synercid** suggest that the incidence of adverse effects in patients with chronic liver insufficiency or cirrhosis was comparable to that in patients with normal hepatic function. However, based on the pharmacokinetic parameters in patients with hepatic cirrhosis, a dosage reduction to 5 mg/kg of **Synercid** is recommended if the tolerability of Synercid at the dose of 7.5 mg/kg is not acceptable. (See **Pharmacokinetics** and **PRECAUTIONS**.)

*Obese Patients:* No dosage adjustment of **Synercid** is required for use in obese patients. (See **Pharmacokinetics**.)

*Pediatric Patients:* Based on the experience in a limited number of pediatric patients in non-comparative trials, no dosage adjustment of **Synercid** is required. (See **PRECAUTIONS**.)

**Preparation and administration of solution:**
1. Reconstitute the single dose vial by slowly adding 5 mL of Dextrose 5% or Sterile Water for injection.
2. Gently swirl the vial by manual rotation without shaking to ensure dissolution of contents while limiting foam formation.

3. Allow the solution to sit for a few minutes until all the foam has disappeared. The resulting solution should be clear. Vials reconstituted in this manner will give a solution of 100 mg/mL. CAUTION: FURTHER DILUTION REQUIRED BEFORE INFUSION.
4. According to the patient's weight, the **Synercid** solution should be added to 250 mL of 5% Dextrose solution. An infusion volume of 100 mL may be used for central line infusions.
5. The desired dose should be administered by intravenous infusion over 60 minutes.

NOTE: As for other parenteral drug products, **Synercid** should be inspected visually for particulate matter prior to administration.

**Incompatibilities: DO NOT DILUTE WITH SALINE SOLUTIONS SINCE SYNERCID IS NOT COMPATIBLE WITH THESE AGENTS.** Synercid should not be mixed with, or physically added to, other drugs since compatibility has not been established.

With intermittent infusion of **Synercid** and other drugs through a common intravenous line, the line should be flushed before and after **Synercid** administration with 5% Dextrose solution.

**Stability and Storage: Before Reconstitution:** The unopened vials should be stored in a refrigerator at 2 to 8°C (36 to 46°F).

**Reconstituted and Infusions Solutions:** Since **Synercid** contains no antibacterial preservative, it should be reconstituted under strict aseptic conditions (*e.g.* Laminar Air Flow Hood). The reconstituted solution should be diluted within 30 minutes. Vials are for single use. The storage time of the diluted solution should be as short as possible to minimize the risk of microbial contamination. Stability of the diluted solution prior to the infusion is established as 5 hours at room temperature or 54 hours if stored under refrigeration 2 to 8°C (36 to 46°F). The solution should not be frozen.

## HOW SUPPLIED

**Synercid** is supplied as a sterile freeze-dried pyrogen-free preparation in single-dose 10 mL type I glass vials serrated with aluminum body with dark blue flip-off cap.

Each vial contains sufficient quinupristin/dalfopristin to deliver 500 mg for intravenous administration. NDC 0075-9051-25 in trays of 25 vials.

## CLINICAL STUDIES

Non-comparative clinical trials were conducted in eight countries. **Synercid** was used for infections due to Gram-positive pathogens for which no other treatment option was appropriate because of *in vitro* resistance of the infecting organism to all available appropriate agents, or because of the patient's intolerance of, or failure on, all available appropriate agents.

The overall response rate, which represents a combination of the clinical success rate (cure plus improvement) and the bacteriologic success rate (eradicated plus presumed eradicated), for the clinically evaluable and bacteriologically evaluable populations, respectively, by indication are as follows:

| **Indications (non-comparative trials)** | **Clinically Evaluable Population** | **Bacteriologically Evaluable Population** |
|---|---|---|
| **All Patients** | 72.2% (312/432) | 68.0% (230/338) |
| Intra-Abdominal Infections | 65.9% (91/138) | 61.6% (69/112) |
| Bacteremia of Unknown Origin | 70.4% (57/81) | 64.6% (42/65) |
| Central Catheter-Related Bacteremia | 82.9% (34/41) | 78.1% (25/32) |
| Skin and Skin Structure Infection | 74.5% (38/51) | 71.1% (27/38) |
| Urinary Tract Infection | 84.8% (39/46) | 85.3% (29/34) |
| Bone and Joint Infection | 81.1% (30/37) | 80.8% (21/26) |
| Respiratory Tract Infections | 76.9% (10/13) | 66.7% (6/9) |

| **Indications** | **Clinically Evaluable Population** | **Bacteriologically Evaluable Population** |
|---|---|---|
| **All Vancomycin-resistant *Enterococcus faecium* infections** | 69.8% (250/358) | 65.5% (186/284) |

| **Indications** | **Clinically Evaluable Population** | **Bacteriologically Evaluable Population** |
|---|---|---|
| **All *Staphylococcus aureus* Infections (including methicillin-susceptible and methicillin-resistant strains)** | 85.3% (29/34) | 81.8% (18/22) |

In order to interpret the breakpoints, clinical and bacteriologic patient outcomes versus MICs are given below:

Correlation of Satisfactory Patient Outcomes and Synercid MICs of Baseline Pathogens[a] from Non-Comparative trials[b] (Clinically and Bacteriologically Evaluable Population) (N/Total N (%))

| | Clinical | | | | Bacteriological | | | |
|---|---|---|---|---|---|---|---|---|
| | Success[c] | | Failure | | Eradication[d] | | Persistence[e] | |
| ≤1 μg/mL | 123/167 | (73.7) | 44/167 | (26.3) | 121/167 | (72.5) | 46/167 | (27.5) |
| ≤2 μg/mL | 131/180 | (72.8) | 49/180 | (27.2) | 129/180 | (71.7) | 51/180 | (28.3) |
| 2 μg/mL | 8/13 | (61.5) | 5/13 | (38.5) | 8/13 | (61.5) | 5/13 | (38.5) |

[a] Includes vancomycin-resistant *E. faecium*, methicillin-sensitive and -resistant *S. aureus*, and other pathogens.
[b] Patients who received Synercid for infections due to Gram-positive pathogens for which no other treatment option was appropriate.
[c] Cure or improvement of clinical signs and symptoms.
[d] Eradication or presumed eradication of baseline pathogen.
[e] Persistence or presumed persistence of baseline pathogen.

At MICs of ≤ 1 or ≤ 2 μg/mL the satisfactory clinical and bacteriological response rates were comparable, *i.e.*, 72 to 74%. At MICs of 2 μg/mL, the correlation was 62% (8/13). At MICs of ≥ 4 μg/mL the correlation was 75% (3/4). However, the number of observations was very small; consequently, results must be interpreted with caution.

Correlation of Satisfactory Patient Outcomes and Synercid MICs of Baseline Pathogens from Comparative trials[a] (Clinically and Bacteriologically Evaluable Population) (N/Total N (%))

| | Clinical | | | | Bacteriological | | | |
|---|---|---|---|---|---|---|---|---|
| | Success[b] | | Failure | | Eradication[c] | | Persistence[d] | |
| ≤1 μg/mL | 192/275 | (69.8)[e] | 83/275 | (30.2) | 199/275 | (72.4) | 76/275 | (27.6) |
| ≤2 μg/mL | 201/286 | (70.3) | 85/286 | (29.7) | 208/286 | (72.7) | 78/286 | (27.3) |
| 2 μg/mL | 9/11 | (81.8) | 2/11 | (18.2) | 9/11 | (81.8) | 2/11 | (18.2) |

[a] Nosocomial pneumonia, complicated skin and skin structure infections, and community-acquired pneumonia.
[b] Cure or improvement of clinical signs and symptoms.
[c] Eradication or presumed eradication of baseline pathogen.
[d] Persistence or presumed persistence of baseline pathogen.
[e] Pathogens assessed include staphylococci (including methicillin-resistant strains), streptococci, enterococci, and *M. catarrhalis*.

At MICs of ≤ 1 or ≤ 2 μg/mL the satisfactory clinical and bacteriological response rates for comparative studies were comparable, *i.e.*, 70 to 74%. At MICs ≥ 4 μg/mL the correlation was 33% (3/9) to 22% (2/9), respectively. However, the number of observations was very small; consequently, results must be interpreted with caution.

**Caution:** Federal law prohibits dispensing without a prescription.

**Keep out of the reach of children.**

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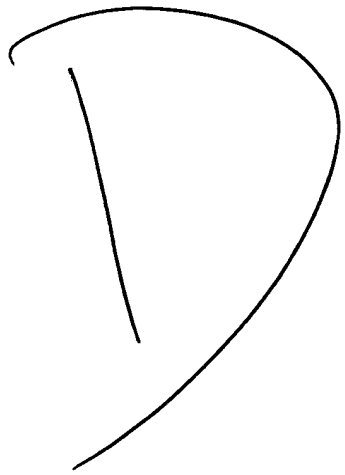

# United States Patent [19]

**Barriere et al.**

[11] **Patent Number: 4,668,669**

[45] **Date of Patent: May 26, 1987**


[54] **PRISTINAMYCIN $II_B$ DERIVATIVES AND COMPOSITIONS CONTAINING THEM**


[75] Inventors: **Jean-Claude Barriere**, Massy; **Claude Cotrel**, Paris; **Jean-Marc Paris**, Vaires sur Marne, all of France

[73] Assignee: **Rhone-Poulenc Sante**, Courbevoie, France



[21] Appl. No.: **817,548**

[22] Filed: **Jan. 10, 1986**

[30] **Foreign Application Priority Data**

Jan. 11, 1985 [FR] France ..... 85 00377

[51] **Int. Cl.**[4] ..... **A61K 31/42**; C07D 498/14; C07K 5/12

[52] **U.S. Cl.** ..... **514/183**; 530/317; 540/455

[58] **Field of Search** ..... 260/239.3 T; 514/183; 540/455; 530/317



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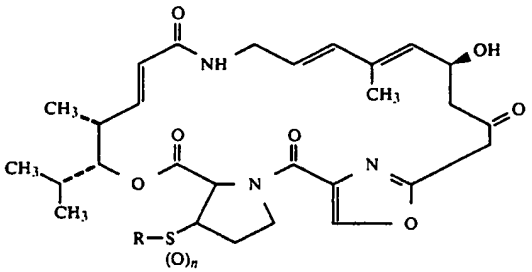
*Primary Examiner*—Robert T. Bond

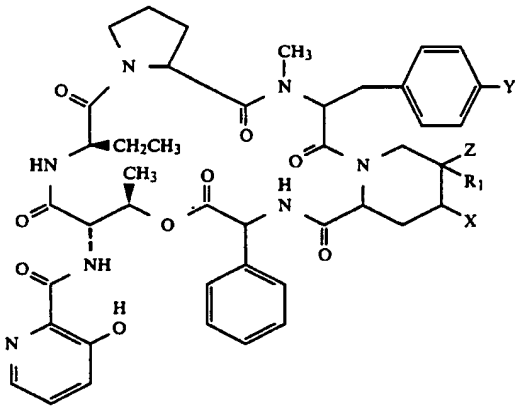
*Attorney, Agent, or Firm*—Stevens, Davis, Miller & Mosher


[57] **ABSTRACT**


Pristinamycin $II_B$ derivatives of formula:



in which R denotes a nitrogen-containing 4 to 7-membered heterocyclic ring optionally substituted by alkyl; or alkyl (2 to 4 C) substituted by 1 or 2 phenyl, cycloalkylamino or N-alkyl-N-cycloalkylamino (3 to 6 ring atoms), alkylamino, dialkylamino or dialkylcarbamoyloxy radicals (the dialkylamino moieties of these 2 latter radicals being capable of forming a 4 to 7-membered cyclic ring optionally substituted by alkyl) or substituted by 1 or 2 nitrogen-containing 4 to 7 membered heterocyclic rings, optionally substituted by alkyl, at least one of the above substituents being a nitrogen-containing substituent capable of forming salts and n is 1 or 2, all the alkyls being linear or branched and containing (unless stated otherwise) 1 to 10 carbon atoms, their isomers, their salts and their preparation. These compounds, optionally in combination with known synergistins or synergistins of formula:



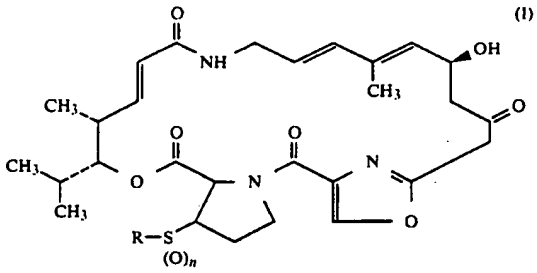
are useful as antimicrobial agents.


**10 Claims, No Drawings**

# PRISTINAMYCIN $II_B$ DERIVATIVES AND COMPOSITIONS CONTAINING THEM

This invention relates to pristinamycin $II_B$ derivatives their preparation, and compositions containing them.

The present invention provides new pristinamycin $II_B$ derivatives, of the formula:



(I)

and their acid addition salts, in which R denotes: either a nitrogen-containing 4 to 7-membered heterocyclic ring radical, which may contain 1 or more other hetero atoms chosen from nitrogen, oxygen and sulphur in the form of sulphoxide or sulphone, and unsubstituted or substituted by alkyl; or alkyl of 2 to 4 carbon atoms substituted by 1 or 2 radicals chosen from phenyl, cycloalkylamino of 3 to 6 ring atoms, N-alkyl-N-cycloalkylamino of 3 to 6 ring atoms, alkylamino, dialkylamino and dialkylcarbamoyloxy, the alkyl parts of these 2 latter radicals being unjoined or joined to form, with the nitrogen atom to which they are attached, a saturated or unsaturated 4 to 7-membered heterocyclic ring which may contain another hetero atom chosen from nitrogen, oxygen and sulphur in the form of sulphoxide or sulphone, and unsubstituted or substituted by alkyl, or alkyl of 2 to 4 carbon atoms substituted by one or more nitrogen-containing, 4 to 7-membered heterocyclic rings which may contain 1 or 2 other hetero atoms chosen from nitrogen, oxygen and sulphur in the form of sulphoxide or sulphone, and unsubstituted or substituted by alkyl, these heterocyclic rings being linked to the alkyl by a carbon atom of the ring, at least one of the substituents carried by the said alkyl chain being a nitrogen-containing substituent capable of forming salts, and n is 1 or 2. The alkyl radicals and moieties referred to above are linear or branched and, unless mentioned otherwise, contain 1 to 10 carbon atoms.

The products of formula (I) have isomeric forms and their isomers and their mixtures are included within the scope of the present invention.

When R denotes a heterocyclic radical, this radical can be, for example: 3-azetidinyl, 3-pyrrolidinyl, 3- or 4-piperidyl or 3- or 4-azepinyl.

When R denotes an alkyl radical substituted by a heterocyclic ring radical, the heterocyclic ring radical can be chosen, for example, from the radicals listed above or the 2-azetidinyl, 2-pyrrolidinyl, 2-piperidyl, 2-azepinyl, piperazinyl, 4-alkylpiperazinyl, quinolyl, isoquinolyl or imidazolyl radicals.

When R contains a dialkylamino or dialkylcarbamoyloxy radical in which the alkyl moieties form a heterocyclic ring with the nitrogen atom to which they are attached, this ring can be chosen, for example, from: 1-azetidinyl, 1-pyrrolidinyl, piperidino, 1-azepinyl, morpholino, thiomorpholino in the form of sulphoxide or sulphone, 1-piperazinyl, 4-alkyl-1-piperazinyl, N-alkyl-1-homopiperazinyl, or 1-imidazolyl.

The following compounds of general formula (I) can be mentioned, in particular, by way of example:

26-(3-azetidinyl)sulphinylpristinamycin $II_B$
26-(1-methyl-3-azetidinyl)sulphinylpristinamycin $II_B$
26-(1-ethyl-3-azetidinyl)sulphinylpristinamycin $II_B$
26-(1-isopropyl-3-azetidinyl)sulphinylpristinamycin $II_B$
26-(3-pyrrolidinyl)sulphinylpristinamycin $II_B$
26-(1-methyl-3-pyrrolidinyl)sulphinylpristinamycin $II_B$
26-(1-ethyl-3-pyrrolidinyl)sulphinylpristinamycin $II_B$
26-(1-isopropyl-3-pyrrolidinyl)sulphinylpristinamycin II
26-(3-piperidyl)sulphinylpristinamycin $II_B$
26-(1-methyl-3-piperidyl)sulphinylpristinamycin $II_B$
26-(1-ethyl-3-piperidyl)sulphinylpristinamycin $II_B$
26-(4-piperidyl)sulphinylpristinamycin $II_B$
26-(1-methyl-4-piperidyl)sulphinylpristinamycin $II_B$
26-(1-ethyl-4-piperidyl)sulphinylpristinamycin $II_B$
26-(3-azepinyl)sulphinylpristinamycin $II_B$
26-(4-azepinyl)sulphinylpristinamycin $II_B$
26-(2-cyclopropylaminoethyl)sulphinylpristinamycin $II_B$
26-(2-cyclobutylaminoethyl)sulphinylpristinamycin $II_B$
26-(2-cyclopentylaminoethyl)sulphinylpristinamycin $II_B$
26-(2-cyclohexylaminoethyl)sulphinylpristinamycin $II_B$
26-(N-cyclohexyl-N-methyl-2-aminoethyl)sulphinylpristinamycin $II_B$
26-(2-methylaminoethyl)sulphinylpristinamycin $II_B$
26-(2-ethylaminoethyl)sulphinylpristinamycin $II_B$
26-(2-propylaminoethyl)sulphinylpristinamycin $II_B$
26-(2-isopropylaminoethyl)sulphinylpristinamycin $II_B$
26-(2-butylaminoethyl)sulphinylpristinamycin $II_B$
26-(2-isobutylaminoethyl)sulphinylpristinamycin $II_B$
26-(2-n-decylaminoethyl)sulphinylpristinamycin $II_B$
26-(dimethylaminoethyl)sulphinylpristinamycin $II_B$
26-(2-diethylaminoethyl)sulphinylpristinamycin $II_B$
26-(2-dipropylaminoethyl)sulphinylpristinamycin $II_B$
26-(2-diisopropylaminoethyl)sulphinylpristinamycin $II_B$
26-(2-dibutylaminoethyl)sulphinylpristinamycin $II_B$
26-(2-diisobutylaminoethyl)sulphinylpristinamycin $II_B$
26-(N-ethyl-N-methyl-2-aminoethyl)sulphinylpristinamycin $II_B$
26-[2-(1-azetidinyl)ethyl]sulphinylpristinamycin $II_B$
26-[2-(1-pyrrolidinyl)ethyl]sulphinylpristinamycin $II_B$
26-(2-piperidinoethyl)sulphinylpristinamycin $II_B$
26-[2-(1-azepinyl)ethyl]sulphinylpristinamycin $II_B$
26-(2-morpholinoethyl)sulphinylpristinamycin $II_B$
26-[2-(1-piperazinyl)ethyl]sulphinylpristinamycin $II_B$
26-[2-(4-methyl-1-piperazinyl)ethyl]sulphinylpristinamycin $II_B$
26-[2-(4-methyl-1-homopiperazinyl)ethyl]sulphinylpristinamycin $II_B$
26-[2-(1-imidazolyl)ethyl]sulphinylpristinamycin $II_B$
26-(2-dimethylaminocarbamoyloxyethyl)sulphinylpristinamycin $II_B$
26-(2-diethylaminocarbamoyloxyethyl)sulphinylpristinamycin $II_B$
26-(2-diisopropylaminocarbamoyloxyethyl)sulphinylpristinamycin $II_B$

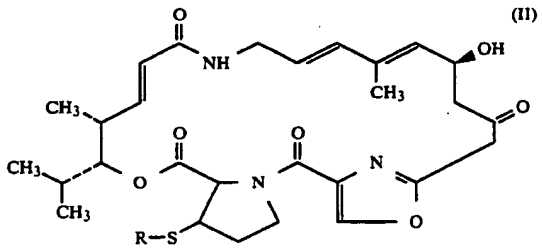
26-[2-(4-methyl-1-piperazinyl)carbamoyloxyethyl]sulphinylpristinamycin $II_B$
26-[2-(2-azetidinyl)ethyl]sulphinylpristinamycin $II_B$
26-[2-(3-azetidinyl)ethyl]sulphinylpristinamycin $II_B$
26-[2-(2-pyrrolidinyl)ethyl]sulphinylpristinamycin $II_B$
26-[2-(3-pyrrolidinyl)ethyl]sulphinylpristinamycin $II_B$
26-[2-(2-piperidyl)ethyl]sulphinylpristinamycin $II_B$
26-[2-(3-piperidyl)ethyl]sulphinylpristinamycin $II_B$
26-[2-(4-piperidyl)ethyl]sulphinylpristinamycin $II_B$
26-[2-(2-azepinyl)ethyl]sulphinylpristinamycin $II_B$
26-[2-(3-azepinyl)ethyl]sulphinylpristinamycin $II_B$
26-[2-(4-azepinyl)ethyl]sulphinylpristinamycin $II_B$
26-[2-(3-quinolyl)ethyl]sulphinylpristinamycin $II_B$
26-[2-(4-quinolyl)ethyl]sulphinylpristinamycin $II_B$
26-[2-(1,2,3,4-tetrahydro-2-isoquinolyl)ethyl]sulphinylpristinamycin $II_B$
26-82-(1-isoquinolyl)ethyl]sulphinylpristinamycin $II_B$
26-(2-imidazolylethyl)sulphinylpristinamycin $II_B$
26-(2-cyclopropylamino-1-methylethyl)sulphinylpristinamycin $II_B$
26-(2-cyclobutylamino-1-methylethyl)sulphinylpristinamycin $II_B$
26-(2-cyclopentylamino-1-methylethyl)sulphinylpristinamycin $II_B$
26-(cyclohexylamino-1-methylethyl)sulphinylpristinamycin $II_B$
26-[2-(N-cyclohexyl-N-methyl-amino)-1-methylethyl]-sulphinylpristinamycin $II_B$
26-(2-methylamino-1-methylethyl)sulphinylpristinamycin $II_B$
26-(2-ethylamino-1-methylethyl)sulphinylpristinamycin $II_B$
26-(1-methyl-2-propylaminoethyl)sulphinylpristinamycin $II_B$
26-(2-isopropylamino-1-methylethyl)sulphinylpristinamycin $II_B$
26-(2-butylamino-1-methylethyl)sulphinylpristinamycin $II_B$
26-(2-isobutylamino-1-methylethyl)sulphinylpristinamycin $II_B$
26-(1-methyl-2-n-decylaminoethyl)sulphinylpristinamycin $II_B$
26-(2-dimethylamino-1-methylethyl)sulphinylpristinamycin $II_B$
26-(2-diethylamino-1-methylethyl)sulphinylpristinamycin $II_B$
26-(2-dipropylamino-1-methylethyl)sulphinylpristinamycin $II_B$
26-(2-diisopropylamino-1-methylethyl)sulphinylpristinamycin $II_B$
26-(2-dibutylamino-1-methylethyl)sulphinylpristinamycin $II_B$
26-(2-diisobutylamino-1-methylethyl)sulphinylpristinamycin $II_B$
26-[2-(N-ethyl-N-methyl-amino)-1-methylethyl]sulphinylpristinamycin $II_B$
26-[2-(1-azetidinyl)-1-methylethyl]sulphinylpristinamycin $II_B$
26-[1-methyl-2-(1-pyrrolidinyl)ethyl]sulphinylpristinamycin $II_B$
26-(1-methyl-2-piperidinoethyl)sulphinylpristinamycin $II_B$
26-[2-(1-azepinyl)-1-methylethyl]sulphinylpristinamycin $II_B$
26-(1-methyl-2-morpholinoethyl)sulphinylpristinamycin $II_B$
26-[1-methyl-2-(1-piperazinyl)ethyl]sulphinylpristinamycin $II_B$
26-[2-(4-methyl-1-piperazinyl)-1-methylethyl]sulphinylpristinamycin $II_B$
26-[2-(4-methyl-1-homopiperazinyl)-1-methylethyl]sulphinylpristinamycin $II_B$
26-[2-(1-imidazolyl)-1-methylethyl]sulphinylpristinamycin $II_B$ 26-(2-dimethylaminocarbamoyloxy-1-methylethyl)sulphinylpristinamycin $II_B$
26-(2-diethylaminocarbamoyloxy-1-methylethyl)sulphinylpristinamycin $II_B$
26-(2-diisopropylaminocarbamoyloxy-1-methylethyl)-sulphinylpristinamycin $II_B$
26-[2-(4-methyl-1-piperazinyl)carbamoyloxy-1-methylethyl]sulphinylpristinamycin $II_B$
26-[2-(2-azetidinyl)-1-methylethyl]sulphinylpristinamycin $II_B$
26-[2-(3-azetidinyl)-1-methylethyl]sulphinylpristinamycin $II_B$
26-[1-methyl-2-(2-pyrrolidinyl)ethyl]sulphinylpristinamycin $II_B$
26-[1-methyl-2-(3-pyrrolidinyl)ethyl]sulphinylpristinamycin $II_B$
26-[1-methyl-2-(2-piperidyl)ethyl]sulphinylpristinamycin $II_B$
26-[1-methyl-2-(3-piperidyl)ethyl]sulphinylpristinamycin $II_B$
26-[1-methyl-2-(4-piperidyl)ethyl]sulphinylpristinamycin $II_B$
26-[2-(2-azepinyl)-1-methylethyl]sulphinylpristinamycin $II_B$
26-[2-(3-azepinyl)-1-methylethyl]sulphinylpristinamycin $II_B$
26-[2-(4-azepinyl)-1-methylethyl]sulphinylpristinamycin $II_B$
26-[1-methyl-2-(3-quinolyl)ethyl]sulphinylpristinamycin $II_B$
26-[1-methyl-2-(4-quinolyl)ethyl]sulphinylpristinamycin $II_B$
26-[1-methyl-2-(1,2,3,4-tetrahydro-2-isoquinolyl)ethyl]-sulphinylpristinamycin $II_B$
26-[2-(1-isoquinolyl)-1-methylethyl]sulphinylpristinamycin $II_B$
26-(2-imidazolyl-1-methylethyl)sulphinylpristinamycin IIB
26-(2-cyclopropylamino-2-methylethyl)sulphinylpristinamycin $II_B$
26-(2-cyclobutylamino-2-methylethyl)sulphinylpristinamycin $II_B$
26-(2-cyclopentylamino-2-methylethyl)sulphinylpristinamycin $II_B$
26-(2-cyclohexylamino-2-methylethyl)sulphinylpristinamycin $II_B$
26-[2-(N-cyclohexyl-N-methylamino)-2-methylethyl]-sulphinylpristinamycin $II_B$
26-(2-methylamino-2-methylethyl)sulphinylpristinamycin $II_B$
26-(2-ethylamino-2-methylethyl)sulphinylpristinamycin $II_B$

26-(2-methyl-2-propylaminoethyl)sulphinylpristinamycin $II_B$
26-(2-isopropylamino-2-methylethyl)sulphinylpristinamycin $II_B$
26-(2-butylamino-2-methylethyl)sulphinylpristinamycin $II_B$
26-(2-isobutylamino-2-methylethyl)sulphinylpristinamycin $II_B$
26-(2-methyl-2-n-decylaminoethyl)sulphinylpristinamycin $II_B$
26-(2-dimethylamino-2-methylethyl)sulphinylpristinamycin $II_B$
26-(2-diethylamino-2-methylethyl)sulphinylpristinamycin $II_B$
26-(2-dipropylamino-2-methylethyl)sulphinylpristinamycin $II_B$
26-(2-diisopropylamino-2-methylethyl)sulphinylpristinamycin $II_B$
26-(2-dibutylamino-2-methylethyl)sulphinylpristinamycin $II_B$
26-(2-diisobutylamino-2-methylethyl)sulphinylpristinamycin $II_B$
26-[2-(N-ethyl-N-methyl-amino)-2-methylethyl]sulfinylpristinamycin $II_B$
26-[2-(1-azetidinyl)-2-methylethyl]sulphinylpristinamycin $II_B$
26-[2-methyl-2-(1-pyrrolidinyl)ethyl]sulphinylpristinamycin $II_B$
26-(2-methyl-2-piperidinoethyl)sulphinylpristinamycin IIB
26-[2-(1-azepinyl)-2-methylethyl]sulphinylpristinamycin $II_B$
26-(2-methyl-2-morpholinoethyl)sulphinylpristinamycin $II_B$
26-[2-methyl-2-(1-piperazinyl)ethyl]sulphinylpristinamycin $II_B$
26-[2-(4-methyl)-1-piperazinyl)-2-methylethyl]sulphinylpristinamycin $II_B$
26-[2-(4-methyl-1-homopiperazinyl)-2-methylethyl]sulphinylpristinamycin $II_B$
26-[2-(1-imidazolyl)-2-methylethyl]sulphinylpristinamycin $II_B$
26-(2-dimethylaminocarbamoyloxy-2-methylethyl)sulphinylpristinamycin $II_B$
26-(2-diethylaminocarbamoyloxy-2-methylethyl)sulphinylpristinamycin $II_B$
26-(2-diisopropylaminocarbamoyloxy-2-methylethyl)-sulphinylpristinamycin $II_B$
26-[2-(4-methyl-1-piperazinyl)carbamoyloxy-2-methylethyl]sulphinylpristinamycin $II_B$
26-[2-(2-azetidinyl)-2-methylethyl]sulphinylpristinamycin $II_B$
26-[2-(3-azetidinyl)-2-methylethyl]sulphinylpristinamycin $II_B$
26-[2-methyl-2-(2-pyrrolidinyl)ethyl]sulphinylpristinamycin $II_B$
26-[2-methyl-2-(3-pyrrolidinyl)ethyl]sulphinylpristinamycin $II_B$
26-[2-methyl-2-(2-piperidyl)ethyl]sulphinylpristinamycin $II_B$
26-[2-methyl-2-(3-piperidyl)ethyl]sulphinylpristinamycin $II_B$
26-[2-methyl-2-(4-piperidyl)ethyl]sulphinylpristinamycin $II_B$
26-[2-(2-azepinyl)-2-methylethyl]sulphinylpristinamycin $II_B$
26-[2-(3-azepinyl)-2-methylethyl]sulphinylpristinamycin $II_B$
26-[2-(4-azepinyl)-2-methylethyl]sulphinylpristinamycin $II_B$
26-[2-methyl-2-(3-quinolyl)ethyl]sulphinylpristinamycin $II_B$
26-[2-methyl-2-(4-quinolyl)ethyl]sulphinylpristinamycin $II_B$
26-[2-methyl-2-(1,2,3,4-tetrahydro-2-isoquinolyl)ethyl]-sulphinylpristinamycin $II_B$
26-[2-(1-isoquinolyl)-2-methylethyl]sulphinylpristinamycin $II_B$
26-(imidazolyl-2-methylethyl)sulphinylpristinamycin $II_B$
26-(2-dimethylamino-3-phenylpropyl)sulphinylpristinainamycin $II_B$
26-(2-dimethylaminobutyl)sulphinylpristinamycin $II_B$
26-(3-azetidinyl)sulphonylpristinamycin $II_B$
26-(1-methyl-3-azetidinyl)sulphonylpristinamycin $II_B$
26-(1-ethyl-3-azetidinyl)sulphonylpristinamycin $II_B$
26-(1-isopropyl-3-azetidinyl)sulphonylpristinamycin $II_B$
26-(3-pyrrolidinyl)sulphonylpristinamycin $II_B$
26-(1-methyl-3-pyrrolidinyl)sulphonylpristinamycin $II_B$
26-(1-ethyl-3-pyrrolidinyl)sulphonylpristinamycin $II_B$
26-(1-isopropyl-3-pyrrolidinyl)sulphonylpristinamycin $II_B$
26-(3-piperidyl)sulphonylpristinamycin $II_B$
26-(1-methyl-3-piperidyl)sulphonylpristinamycin $II_B$
26(1-ethyl-3-piperidyl)sulphonylpristinamycin $II_B$
26-(4-piperidyl)sulphonylpristinamycin $II_B$
26-(1-methyl-4-piperidyl)sulphonylpristinamycin $II_B$
26-(1-ethyl-4-piperidyl)sulphonylpristinamycin $II_B$
26-(3-azepinyl)sulphonylpristinamycin $II_B$
26-(4-azepinyl)sulphonylpristinamycin $II_B$
26-(2-cyclopropylaminoethyl)sulphonylpristinamycin $II_B$
26-(2-cyclobutylaminoethyl)sulphonylpristinamycin $II_B$
26-(2-cyclopentylaminoethyl)sulphonylpristinamycin $II_B$
26-(2-cyclohexylaminoethyl)sulphonylpristinamycin $II_B$
26-(N-cyclohexyl-N-methyl-2-aminoethyl)sulphonylpristinamycin $II_B$
26-(2-methylaminoethyl)sulphonylpristinamycin $II_B$
26-(2-ethylaminoethyl)sulphonylpristinamycin $II_B$
26-(2-propylaminoethyl)sulphonylpristinamycin $II_B$
26-(2-isopropylaminoethyl)sulphonylpristinamycin $II_B$
26-(2-butylaminoethyl)sulphonylpristinamycin $II_B$
26-(2-isobutylaminoethyl)sulphonylpristinamycin $II_B$
26-(2-n-decylaminoethyl)sulphonylpristinamycin $II_B$
26-(2-dimethylaminoethyl)sulphonylpristinamycin $II_B$
26-(2-diethylaminoethyl)sulphonylpristinamycin $II_B$
26-(2-dipropylaminoethyl)sulphonylpristinamycin $II_B$
26-(2-diisopropylaminoethyl)sulphonylpristinamycin $II_B$
26-(2-dibutylaminoethyl)sulphonylpristinamycin $II_B$
26-(2-diisobutylaminoethyl)sulphonylpristinamycin $II_B$
26-(N-ethyl-N-methyl-2-aminoethyl)sulphonylpristinamycin $II_B$

26-[2-(1-azetidinyl)ethyl]sulphonylpristinamycin $II_B$
26-[2-(1-pyrrolidinyl)ethyl]sulphonylpristinamycin $II_B$
26-(2-piperidinoethyl)sulphonylpristinamycin $II_B$
26-[2-(1-azepinyl)ethyl]sulphonylpristinamycin $II_B$
26-(2-morpholinoethyl)sulphonylpristinamycin $II_B$
26-[2-(1-piperazinyl)ethyl]sulphonylpristinamycin $II_B$
26-[2-(4-methyl-1-piperazinyl)ethyl]sulphonylpristinamycin $II_B$
26-[2-(4-methyl-1-homopiperazinyl)ethyl]sulphonylpristinamycin $II_B$
26-[2-(1-imidazolyl)ethyl]sulphonylpristinamycin $II_B$
26-(2-dimethylaminocarbamoyloxyethyl)sulphonylpristinamycin $II_B$
26-(2-diethylaminocarbamoyloxyethyl)sulphonylpristinamycin $II_B$
26-(2-diisopropylaminocarbamoyloxyethyl)sulphonylpristinamycin $II_B$
26-[2-(4-methyl-1-piperazinyl)carbamoyloxyethyl]sulphonylpristinamycin $II_B$
26-[2-(2-azetidinyl)ethyl]sulphonylpristinamycin $II_B$
26-[2-(3-azetidinyl)ethyl]sulphonylpristinamycin $II_B$
26-[2-(2-pyrrolidinyl)ethyl]sulphonylpristinamycin $II_B$
26-[2-(3-pyrrolidinyl)ethyl]sulphonylpristinamycin $II_B$
26-[2-(2-piperidyl)ethyl]sulphonylpristinamycin $II_B$
26-[2-(3-piperidyl)ethyl]sulphonylpristinamycin $II_B$
26-[2-(4-piperidyl)ethyl]sulphonylpristinamycin $II_B$
26-[2-(2-azepinyl)ethyl]sulphonylpristinamycin $II_B$
26-[2-(3-azepinyl)ethyl]sulphonylpristinamycin $II_B$
26-[2-(4-azepinyl)ethyl]sulphonylpristinamycin $II_B$
26-[2-(3-quinolyl)ethyl]sulphonylpristinamycin $II_B$
26-[2-(4-quinolyl)ethyl]sulphonylpristinamycin $II_B$
26-[2-(1,2,3,4-tetrahydro-2-isoquinolyl)ethyl]sulphonylpristinamycin $II_B$
26-[2-(1-isoquinolyl)ethyl]sulphonylpristinamycin $II_B$
26-(2-imidazolylethyl)sulphonylpristinamycin $II_B$
26-(2-cyclopropylamino-1-methylethyl)sulphonylpristinamycin $II_B$
26-(2-cyclobutylamino-1-methylethyl)sulphonylpristinamycin $II_B$
26-(2-cyclopentylamino-1-methylethyl)sulphonylpristinamycin $II_B$
26-(2-cyclohexylamino-1-methylethyl)sulphonylpristinamycin $II_B$
26-[2-(N-cyclohexyl-N-methylamino)-1-methylethyl)-sulphonylpristinamycin $II_B$
26-(2-methylamino-1-methylethyl)sulphonylpristinamycin $II_B$
26-(2-ethylamino-1-methylethyl)sulphonylpristinamycin $II_B$
26-(1-methyl-2-propylaminoethyl)sulphonylpristinamycin $II_B$
26-(2-isopropylamino-1-methylethyl)sulphonylpristinamycin $II_B$
26-(2-butylamino-1-methylethyl)sulphonylpristinamycin $II_B$
26-(2-isobutylamino-1-methylethyl)sulphonylpristinamycin $II_B$
26-(1-methyl-2-n-decylaminoethyl)sulphonylpristinamycin $II_B$
26-(2-dimethylamino-1-methylethyl)sulphonylpristinamycin $II_B$
26-(2-diethylamino-1-methylethyl)sulphonylpristinamycin $II_B$
26-(2-dipropylamino-1-methylethyl)sulphonylpristinamycin $II_B$
26-(2-diisopropylamino-1-methylethyl)sulphonylpristinamycin $II_B$
26-(2-dibutylamino-1-methylethyl)sulphonylpristinamycin $II_B$
26-(2-diisobutylamino-1-methylethyl)sulphonylpristinamycin $II_B$
26-[2-(N-ethyl-N-methyl-amino)-1-methylethyl[sulphonylpristinamycin $II_B$
26-[2-81-(azetidinyl)-1-methylethyl]sulphonylpristinamycin $II_B$
26-[1-methyl-2-(1-pyrrolidinyl)ethyl]sulphonylpristinamycin $II_B$
26-(1-methyl-2-piperidinoethyl)sulphonylpristinamycin $II_B$
26-[2-(1-azepinyl)-1-methylethyl]sulphonylpristinamycin $II_B$
26-(1-methyl-2-morpholinoethyl)sulphonylpristinamycin $II_B$
26-[1-methyl-2-(1-piperazinyl)ethyl]sulphonylpristinamycin $II_B$
26-[2-(4-methyl-1-piperazinyl)-1-methylethyl]sulphonylpristinamycin $II_B$
26-[2-(4-methyl-1-homopiperazinyl)-1-methylethyl]sulphonylpristinamycin $II_B$
26-[2-(1-imidazolyl)-1-methylethyl]sulphonylpristinamycin $II_B$
26-(2-dimethylaminocarbamoyloxy-1-methylethyl)sulphonylpristinamycin $II_B$
26-(2-diethylaminocarbamoyloxy)-1-methylethyl)-sulphonylpristinamycin $II_B$
26-(2-diisopropylaminocarbamoyloxy-1-methylethyl)-sulphonylpristinamycin $II_B$
26-[2-(4-methyl-1-piperazinyl)carbamoyloxy-1-methylethyl]sulphonylpristinamycin $II_B$
26-[2-(2-azetidinyl)-1-methylethyl]sulphonylpristinamycin $II_B$
26-[2-(3-azetidinyl)-1-methylethyl]sulphonylpristinamycin $II_B$
26-[1-methyl-2-(2-pyrrolidinyl)ethyl]sulphonylpristinamycin $II_B$
26-[1-methyl-2-(3-pyrrolidinyl)ethyl]sulphonylpristinamycin $II_B$
26-[1-methyl-2-(2-piperidyl)ethyl]sulphonylpristinamycin $II_B$
26-[1-methyl-2-(3-piperidyl)ethyl]sulphonylpristinamycin $II_B$
26-[1-methyl-2-(4-piperidyl)ethyl]sulphonylpristinamycin $II_B$
26-[2-(2-azepinyl)-1-methylethyl]sulphonylpristinamycin $II_B$
26-[2-(3-azepinyl)-1-methylethyl]sulphonylpristinamycin $II_B$
26-[2-(4-azepinyl)-1-methylethyl]sulphonylpristinamycin $II_B$
26-[1-methyl-2-(3-quinolyl)ethyl]sulphonylpristinamycin $II_B$
26-[1-methyl-2-[4-quinolyl)ethyl]sulphonylpristinamycin $II_B$
26-[1-methyl-2-(1,2,3,4-tetrahydro-2-isoquinolyl)ethyl]-sulphonylpristinamycin $II_B$

26-[2-(1-isoquinolyl)-1-methylethyl]sulphonylpristinamycin $II_B$
26-(2-imidazolyl-1-methylethyl)sulphonylpristinamycin $II_B$
26-(2-cyclopropylamino-2-methylethyl)sulphonylpristinamycin $II_B$
26-(2-cyclobutylamino-2-methylethyl)sulphonylpristinamycin $II_B$
26-(2-cyclopentylamino-2-methylethyl)sulphonylpristinamycin $II_B$
26-(2-cyclohexylamino-2-methylethyl)sulphonylpristinamycin $II_B$
26-[2-(N-cyclohexyl-N-methyl-amino)-2-methylethyl]-sulphonylpristinamycin $II_B$
26-(2-methylamino-2-methylethyl)sulphonylpristinamycin $II_B$
26-(2-ethylamino-2-methylethyl)sulphonylpristinamycin $II_B$
26-(2-methyl-2-propylaminoethyl)sulphonylpristinamycin $II_B$
26-(2-isopropylamino-2-methylethyl)sulphonylpristinamycin $II_B$
26-(2-butylamino-2-methylethyl)sulphonylpristinamycin $II_B$
26-(2-isobutylamino-2-methylethyl)sulphonylpristinamycin $II_B$
26-(2-methyl-2-n-decylaminoethyl)sulphonylpristinamycin $II_B$
26-(2-dimethylamino-2-methylethyl)sulphonylpristinamycin $II_B$
26-(2-diethylamino-2-methylethyl)sulphonylpristinamycin $II_B$
26-(2-dipropylamino-2-methylethyl)sulphonylpristinamycin $II_B$
26-(2-diisopropylamino-2-methylethyl)sulphonylpristinamycin $II_B$
26-(2-dibutylamino-2-methylethyl)sulphonylpristinamycin $II_B$
26-(2-diisobutylamino-2-methylethyl)sulphonylpristinamycin $II_B$
26-[2-(N-ethyl-N-methyl-amino)-2-methylethyl]-sulphonylpristinamycin $II_B$
26-[2-(1-azetidinyl)-2-methylethyl]sulphonylpristinamycin $II_B$
26-[2-methyl-2-(1-pyrrolidinyl)ethyl]sulphonylpristinamycin $II_B$
26-(2-methyl-2-piperidinoethyl)sulphonylpristinamycin $II_B$
26-[2-(1-azepinyl)-2-methylethyl]sulphonylpristinamycin $II_B$
26-(2-methyl-2-morpholinoethyl)sulphonylpristinamycin $II_B$
26-[2-methyl-2-(1-piperazinyl)ethyl]sulphonylpristinamycin $II_B$
26-[2-(4-methyl-1-piperazinyl)-2-methylethyl]-sulphonylpristinamycin $II_B$
26-[2-(4-methyl-1-homopiperazinyl)-2-methylethyl]-sulphonylpristinamycin $II_B$
26-[2-(1-imidazolyl)-2-methylethyl]sulphonylpristinamycin $II_B$
26-(2-dimethylaminocarbamoyloxy-2-methylethyl)-sulphonylpristinamycin $II_B$
26-(2-diethylaminocarbamoyloxy-2-methylethyl)-sulphonylpristinamycin $II_B$
26-(2-diisopropylaminocarbamoyloxy-2-methylethyl)-sulphonylpristinamycin $II_B$
26-[2-(4-methyl-1-piperazinyl)carbamoyloxy-2-methylethyl]sulphonylpristinamycin $II_B$
26-[2-(2-azetidinyl)-2-methylethyl]sulphonylpristinamycin $II_B$
26-[2-(3-azetidinyl)-2-methylethyl]sulphonylpristinamycin $II_B$
26-[2-methyl-2-(2-pyrrolidinyl)ethyl]sulphonylpristinamycin $II_B$
26-[2-methyl-2-(3-pyrrolidinyl)ethyl]sulphonylpristinamycin $II_B$
26-[2-methyl-2-(2-piperidyl)ethyl]sulphonylpristinamycin $II_B$
26-[2-methyl-2-(3-piperidyl)ethyl]sulphonylpristinamycin $II_B$
26-[2-methyl-2-(4-piperidyl)ethyl]sulphonylpristinamycin $II_B$
26-[2-(2-azepinyl)-2-methylethyl]sulphonylpristinamycin $II_B$
26-[2-(3-azepinyl)-2-methylethyl]sulphonylpristinamycin $II_B$
26-[2-(4-azepinyl)-2-methylethyl]sulphonylpristinamycin $II_B$
26-[2-methyl-2-(3-quinolyl)ethyl]sulphonylpristinamycin $II_B$
26-[2-methyl-2-(4-quinolyl)ethyl]sulphonylpristinamycin $II_B$
26-[2-methyl-2-(1,2,3,4-tetrahydro-2-isoquinolyl)ethyl]-sulphonylpristinamycin $II_B$
26-[2-(1-isoquinolyl)-2-methylethyl]sulphonylpristinamycin $II_B$
26-(2-imidazolyl-2-methylethyl)sulphonylpristinamycin $II_B$
26-(2-dimethylamino-3-phenylpropyl)sulphonylpristinamycin $II_B$
26-(2-dimethylaminobutyl)sulphonylpristinamycin $II_B$

According to the invention, the products of general formula (I) can be prepared by oxidation of a derivative of pristinamycin $II_B$, of its salt or of a protected derivative, of general formula:



(II)

in which R is defined as above, it being understood that in the cases where R contains a sulphur-containing hetero cyclic ring, the sulphur atom can be in the form of a sulphide, sulphoxide or sulphone.

The reaction is generally carried out by means of an oxidizing agent, optionally prepared in situ, in an aqueous medium or in an organic solvent, preferably a chlorinated solvent (methylene chloride, 1,2-dichloroethane or chloroform, for example) or an alcohol (methanol or tert-butanol, for example) or a mixture of these solvents. Optionally the operation can be carried out under nitrogen.

Among the oxidizing agents which are suitable for preparing a product of general formula (I) in which n=1, it is possible to mention organic peracids: percarboxylic or persulphonic acids (for example peracetic, pertrifluoroacetic, performic, perbenzoic, m-chloroperbenzoic, p-nitroperbenzoic, permaleic, monoperphthalic, percamphoric or p-toluenepersulphonic acids) or inorganic peracids (for example periodic or persulphuric acid).

When the intention is to prepare a product of general formula (I) in which n=2, the operation is advantageously carried out in the presence of selenium dioxide and hydrogen peroxide, using the salt of the product of general formula (II), or in the presence of a peracid such as those referred to above, especially pertrifluoroacetic acid, or m-chloroperbenzoic acid.

When the derivative of pristinamycin $II_B$ of general formula (II) is used in the form of a salt, use is made of the salts formed with organic or inorganic acids, preferably with trifluoroacetic, tartaric, acetic, benzoic, or hydrochloric acids.

When the product of general formula (II) is used in the form of a salt or of a protected derivative, the reaction is advantageously carried out at a temperature between −40° and 50° C.

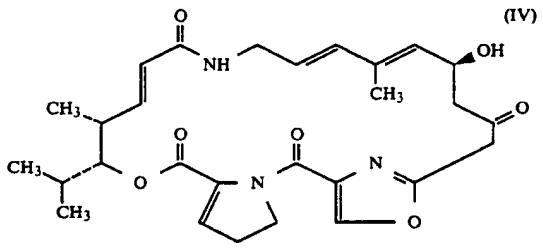
When it is intended to prepare a product of general formula (I) in which n=1, it is also advantageous to operate by starting from the derivative of pristinamycin $II_B$ of general formula (II) in the presence of an alkali metal bicarbonate (for example sodium bicarbonate) at a temperature between −60° and −40° C.

When R contains an alkylamino or cycloalkylamino substituent, it is also possible to utilize a protected derivative of the product of general formula (II). The latter can be protected by any amine-protective group whose introduction and removal do not affect the remainder of the molecule; use is advantageously made of the trifluoroacetyl group which can be removed after the reaction by treatment with an alkali metal bicarbonate (sodium or potassium bicarbonate) in an aqueous solution.

The products of general formula (II) can be prepared by the reaction of a product of general formula:

R—H (III)

in which R is defined as above, with the product of formula:




(IV)

that is to say pristinamycin $II_A$.

The reaction is usually carried out in an organic solvent such as an alcohol such as methanol or ethanol, or a chlorinated solvent such as methylene chloride, 1,2-dichloroethane or chloroform, or in a mixture of these solvents (for example methylene chloride/methanol) at a temperature between −30° and 50° C.

Occasionally it may be advantageous to operate in the presence of a tertiary amine, for example triethylamine, or of an ethanolamine (for example dimethylethanolamine),

A person skilled in the art will understand that, when R denotes a radical containing a secondary amine group capable of interfering with the reaction, this group will need to be protected beforehand, before the product of general formula (III) is reacted with the product of formula (IV). Any usual means which enables a secondary amine function to be blocked in the form of a labile radical can be used for this purpose. It is especially advantageous to use the trifluoroacetyl radical as a blocking radical which can be removed as described above. In such a case, however, it is not absolutely essential to remove the protective radical, and the protected derivative can be used directly in the oxidation reaction.

According to the invention, the products of general formula (I) in which n is equal to 2 can also be prepared by the oxidation of a product of general formula (I) in which n is equal to 1.

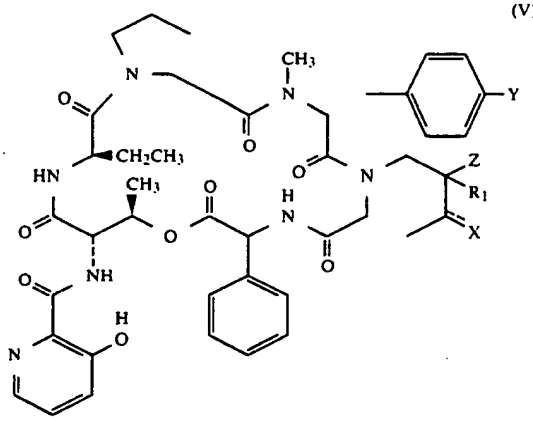
The reaction is carried out under conditions which are similar to the conditions described above for preparing a product of general formula (I) in which n=2 starting from a pristinamycin $II_B$ derivative of general formula (II).

The new products of general formula (I) can be purified by known methods, for example by crystallization, chromatography or successive extractions in an acidic or basic medium. For the person skilled in the art who is aware of the sensitivity of synergistins in an alkaline medium, a "basic medium" is understood to mean a medium which is just alkaline enough to liberate the parent substance from its salt of addition with an acid, that is to say a medium whose pH does not exceed 8.

It is well known that the synergistins obtained by fermentation constitute products which are greatly sought after by medical practitioners for the treatment of many complaints due to Gram-positive bacteria (of the Staphylococci, Streptococci, pneumococci or enterococci type) and Gram-negative bacteria (of the Haemophilus, gonococci, meningococci type). However, these products have the disadvantage of being insoluble in an aqueous medium and consequently can be administered only by oral route, generally in the form of gelatine capsules, coated pills or tablets. In view of this insolubility, it has hitherto been impossible to use the known synergistins when the patient is unable to swallow; this is the case, in particular, in paediatrics and in reanimation, while the activity spectrum of these products would render them a valuable indication in many circumstances, for example in cases of comatose septicaemias.

The new products according to the invention have the considerable advantage of being capable of being dissolved in water, usually in the form of salts, in usable therapeutic doses, and of enhancing, via a synergism phenomenon, the antibacterial action of pristinamycin $I_A$, virginiamycin S or of derivatives of soluble synergistins of general formula:

(V)



in which Y denotes a hydrogen atom or a dimethylamino radical and

(1) either ═══ denotes a single bond, Z and $R_1$ denote a hydrogen atom and X denotes a radical of general formula:

(VI)

in which:

either $R_2$ denotes a hydrogen atom and $R_3$ denotes a hydroxy or alkyl radical optionally substituted by a carboxy, alkyloxycarbonyl, hydroxy, alkylamino or dialkylamino radical whose alkyl radicals can form, with the nitrogen atom to which they are attached, a 4 to 7-membered hetero-cyclic ring chosen from azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, N-alkylpiperazinyl or azepinyl rings, or $R_3$ denotes a cycloalkyl radical containing 3 to 7 carbon atoms or a saturated 4 to 7-membered heterocyclic ring chosen from the azetidine, pyrrolidine, piperidine and azepine rings, these heterocyclic rings being optionally capable of being substituted by an alkyl radical on the nitrogen atom,

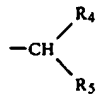
or $R_2$ denotes a formyl or alkylcarbonyl radical and $R_3$ denotes an alkyl radical substituted by a carboxy, alkylamino or dialkylamino radical whose alkyl radicals can form, with the nitrogen atom to which they are attached a 4, to 7-membered heterocyclic ring chosen from azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, N-alkylpiperazinyl or azepinyl ring, or $R_3$ denotes a 4 to 7-membered heterocyclic ring chosen from the azetidine, pyrrolidine, piperidine and azepine rings, these heterocyclic rings being capable of being substituted by an alkyl radical on the nitrogen atom,

or $R_2$ and $R_3$, which are identical or different, denote an alkyl radical optionally substituted by a carboxy, alkyloxycarbonyl, hydroxy, alkylamino or dialkylamino radical whose alkyl radicals optionally form, with the nitrogen atom to which they are attached, a 4 to 7-membered heterocyclic ring chosen from azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, N-alkylpiperazinyl or azepinyl

or $R_2$ and $R_3$ form, together with the nitrogen atom to which they are attached, a 4 to 7-membered heterocyclic ring chosen from the azetidine, pyrrolidine, piperidine, morpholine and piperazine rings, optionally substituted by an alkyl radical,

(2) or ═══ denotes a double bond, X denotes an oxygen atom and Z denotes a radical of general formula:

(VII)



defined as follows:

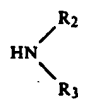
(a) either $R_1$ and $R_5$ each denote a hydrogen atom and $R_4$ denotes a 3-pyrrolidinylthio or 3- or 4-piperidylthio radical (these radicals being optionally substituted by an alkyl radical) or $R_4$ denotes an alkylthio radical substituted by one or two hydroxysulphonyl, alkylamino, or dialkylamino (optionally substituted by a mercapto or dialkylamino radical) radicals, or by one or two rings chosen from piperazino (optionally substituted by an alkyl or mercaptoalkyl radical) morpholino, thiomorpholino, piperidino, 1-pyrrolidinyl, 2-, 3- or 4-piperidyl and 2- or 3-pyrrolidinyl radicals (the latter two rings being optionally substituted by an alkyl radical on the nitrogen atom),

(b) or $R_1$ and $R_5$ together form a valency bond and $R_4$ denotes a 3-pyrrolidinylamino, 3- or 4-piperidylamino, 3-pyrrolidinyloxy, 3- or 4-piperidyloxy, 3-pyrrolidinylthio or 3- or 4-piperidylthio radical (these radicals being optionally substituted by an alkyl radical on the nitrogen atom in the ring), or $R_4$ denotes an alkylamino, alkyloxy or alkylthio radical substituted by one or two hydroxysulphonyl, alkylamino, dialkylamino (optionally substituted by a dialkylamino radical), trialkylammonio or 4- or 5-imidazolyl radicals or by one or two rings chosen from piperazino (optionally substituted by an alkyl or mercapto alkyl radical), morpholino, thiomorpholino, piperidino, 1-pyrrolidinyl, 2-, 3- or 4-piperidinyl and 2- or 3-pyrrolidinyl radical (the last two rings being optionally substituted by an alkyl radical on the nitrogen atom), it being understood that the alkyl radicals and alkyl moieties referring to the symbols of the general formula (V) contain 1 to 5 carbon atoms and form a linear or branched chain.

Some of the derivatives of synergistins of general formula (V) can have isomeric forms. It is to be understood that these isomeric forms as well as their mixtures can be advantageously associated with the products of general formula (I).

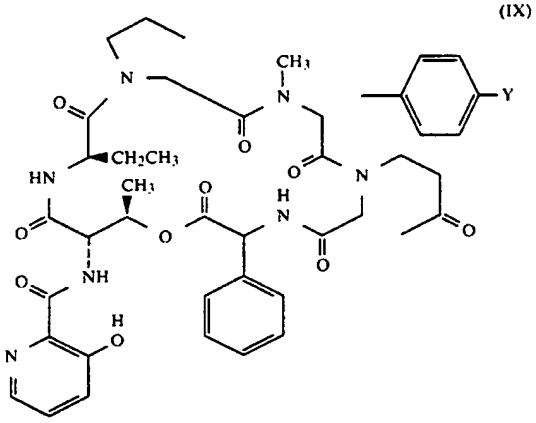
The products of general formula (V) defined as above under (1), with the exception of those in which $R_2$ denotes a formyl or alkylcarbonyl radical, can be prepared by the action of an amine of general formula:

(VIII)



in which $R_2$ and $R_3$ are defined as above, on a synergistin of general formula:

(IX)



in which Y denotes a hydrogen atom (virginiamycin S) or the dimethylamino radical (pristinamycin $I_A$), in the presence of an alkali metal cyanoborohydride.

The operation is generally carried out with an excess of amine of general formula (VIII) in the presence of an alkali metal cyanoborohydride such as sodium cyanoborohydride, in an organic solvent such as an alcohol containing dissolved gaseous hydrogen chloride (methanolic hydrogen chloride or ethanolic hydrogen chloride) at a temperature between 0° C. and the reflux temperature of the reaction mixture, preferably at a temperature in the region of 20° C.

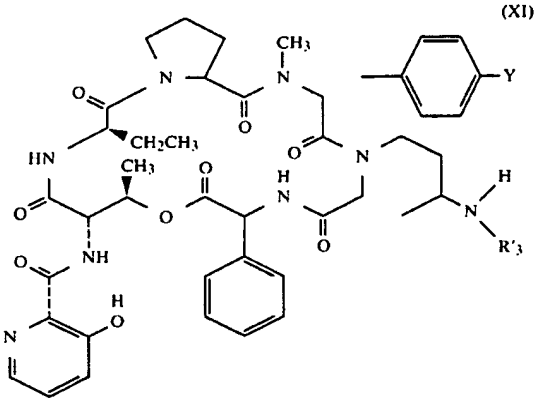
The reaction can be advantageously carried out in the presence of a drying agent such as molecular sieves.

The products of general formula (V) defined as above under (1) in which $R^2$ denotes a formyl or alkylcarbonyl radical and $R_3$ denotes an alkyl radical substituted by a carboxy, alkylamino or dialkylamino radical whose alkyl radicals optionally form, with the nitrogen atom to which they are attached, a 4 to 7-membered heterocyclic ring chosen from azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, alkyl-piperazinyl or azepinyl ring, or denotes a saturated 4 to 7-membered heterocyclic ring chosen from the azetidine, pyrrolidine, piperidine and azepine rings, these heterocyclic rings being capable of being substituted by an alkyl radical on the nitrogen atom, and Y is defined as above, can be prepared by the action of a product of general formula:

$$R_6—CO—Q \qquad (X)$$

in which $R_6$ denotes a hydrogen atom or an alkyl radical and Q denotes a halogen atom or an alkylcarbonyloxy radical, on a product of general formula:

(XI)



in which Y is defined as before and $R'_3$ has the corresponding definition of $R_3$ which is given above.

The reaction is usually carried out in an organic solvent such as pyridine, in a chlorinated solvent (methylene chloride) or an ether (tetrahydrofuran) in the presence of an acid acceptor such as an organic base such as triethylamine or an inorganic base such as an alkali metal carbonate or bicarbonate such as sodium bicarbonate, the operation being carried out at a temperature between 0° and 80° C.

It is to be understood that, when $R'_3$ denotes a radical containing a secondary amine group, the said group must be protected before the product of general formula (X) is reacted with the product of general formula (XI). The protection is carried out under the conditions described earlier for the preparation of the product of the general formula (II).

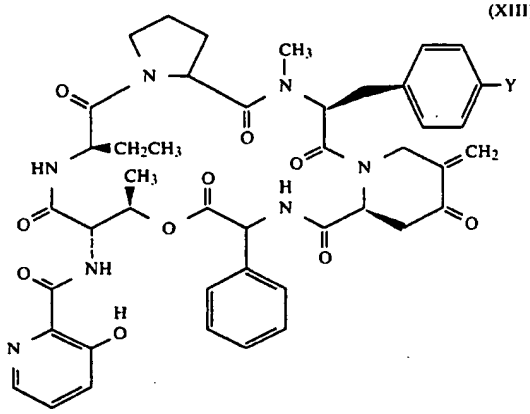
It is also to be understood that, when $R_2$ and/or $R_3$ in the general formula (VIII) denote a radical containing a secondary amine group, the latter must be protected beforehand, before the product of general formula (VIII) is reacted with the product of general formula (IX). The blocking and the deblocking are carried out as described earlier.

The products of general formula (V) defined as before under (2), in which Y is defined as before and the other symbols are defined as before under (2) (a) can be prepared by the action of a product of general formula:

$$R'_4—H \qquad (XII)$$

in which $R'_4$ has the definition of $R_4$ given earlier under (2) (a), on the product of general formula:

(XIII)

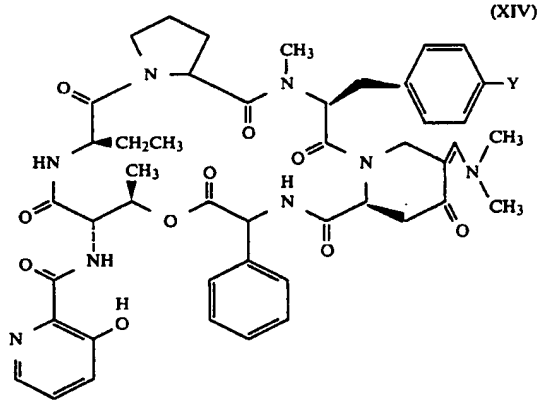


in which Y is defined as before.

The operation is usually carried out in an organic solvent such as an alcohol such as methanol, or a chlorinated solvent such as chloroform, or a mixture of these solvents, at a temperature between 0° C. and the reflux temperature of the reaction mixture, preferably at a temperature in the region of 20° C.

The products of general formula (XIII) can be prepared by the action of an alkali metal borohydride such as sodium cyanoborohydride on a product of general formula:

(XIV)

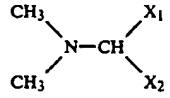


in which Y is defined as before.

The operation is usually carried out in an organic solvent such as an ether such as tetrahydrofuran, or an alcohol, for example isopropanol, in the presence of an acid such as trifluoroacetic acid, at a temperature between 0° C. and the reflux temperature of the reaction mixture, preferably at a temperature in the region of 20° C.

The products of general formula (XIV) can be obtained by the action of a product of formula:

(XV)



in which either $X_1$ denotes an alkyloxy radical and $X_2$ denotes an alkyloxy or dimethylamino radical, or $X_1$ and $X_2$ both denote a dimethylamino radical, on a product of general formula (IX).

In practice, it is advantageous to react tertbutoxybis(-dimethylamino)methane with the product of general formula (IX), the operation being carried out in an organic solvent such as a chlorinated solvent such as 1,2-dichloroethane, or an amide (for example dimethylformamide) at a temperature between 0° and 80° C., preferably at a temperature in the region of 20° C.

The products of general formula (XV) can be prepared according to the methods described by H. Bredereck et al., Chem. Ber., 101, 41 and 3058 (1968) and Chem. Ber., 106, 3725 (1973).

The products of general formula (V) in which Y is defined as before and the other symbols are defined as earlier under (2) (b), except for $R_4$ denoting a 3-pyrrolidinyloxy, 3- or 4-piperidyloxy or alkyloxy radical, optionally substituted as defined under (2) (b), can be prepared by the action of a product of general formula:

$$R''_4—H \qquad (XVI)$$

in which $R''_4$ has the definition of $R_4$ given above, on a product of general formula (XIV) in which Y is defined as earlier.

The reaction is carried out in an organic medium in the presence of an acid (for example acetic acid or a mixture of acetic acid with catalytic quantities of trifluoroacetic acid), in the presence or absence of a solvent, at a temperature beween 0° and 50° C.; preferably at a temperature in the region of 20° C.

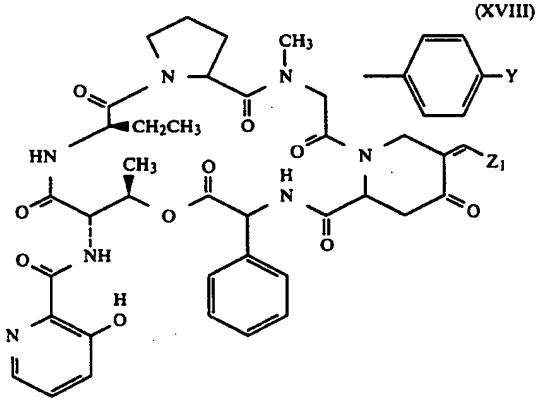
Where applicable, the solvent can be chosen from organic solvents such as ethers (tetrahydrofuran), alcohols (ethanol) and chlorinated solvents (methylene chloride or chloroform, for example).

The products of general formula (V) in which Y is defined as before and the other symbols are defined as earlier under (2) (b) can be prepared by the action of a product of general formula:

$$R'''_4—H \qquad (XVII)$$

in which $R'''_4$ is defined as $R_4$ under (2) (b), on a product of general formula:

(XVIII)



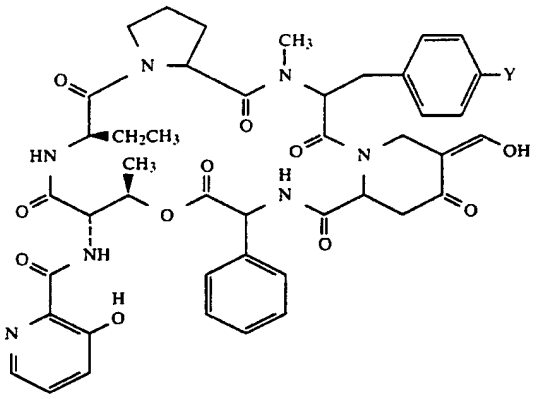
in which Y is defined as before and $Z_1$ denotes a tosyloxy, acetyloxy, trimethylsilyloxy or dialkyloxyphoshoryloxy radical whose alkyl moieties contain 1 to 4 carbon atoms forming a linear or branched chain or $Z_1$ denotes a chlorine atom.

The operation is usually carried out in an organic solvent such as ether such as tetrahydrofuran, an alcohol such as ethanol, or a chlorinated solvent (methylene chloride or chloroform, for example) at a temperature in the region of 20° C. The reaction is carried out in a basic medium, for example in the presence of an alkali metal hydride or an alkali metal alcoholate such as sodium ethoxide or potassium tert-butoxide.

When $R'''_4$ is different from a substituted alkyloxy or (heterocyclic ring radical)oxy radical, it is also possible to operate either in a neutral medium at a temperature between 0° and 50° C., in one of the solvents mentioned above, or in an acetic medium under conditions identical to those described earlier for the action of a product of general formula (XVI) on a product of general formula (XIV).

The products of general formula (XVIII) can be prepared by acid hydrolysis of a product of general formula (XIV) to obtain a product of general formula:

(XIX)



followed:

(α) either by the action of a product of general formula:

$$Z'_1—X \qquad (XX)$$

in which X denotes a halogen atom and $Z'_1$ has the definition given before for $Z_1$, except for denoting a chlorine atom

(β) or by the action of a product of formula:

$$(C_6H_5)_3PCl_2 \qquad (XXI)$$

to obtain a product of general formula (XVIII) in which $Z_1$ denotes a chlorine atom.

The hydrolysis of the product of general formula (XIV) to the product of general formula (XVIII) is carried out by means of an aqueous solution of an inorganic acid such as a 0.1N aqueous solution of hydrochloric acid, the operation being carried out at a temperature in the region of 20° C.

The reaction of the product of general formula (XX) with the product of general formula (XIX) is generally carried out in an organic solvent such as methylene chloride in the presence of an acid-acceptor such as an organic base such as triethylamine, or an inorganic base such as an alkali metal carbonate or bicarbonate, for example sodium or potassium bicarbonate. The operation is generally carried out at a temperature between −20° and +20° C.

The reaction of the product of general formula (XXI) with the product of general formula (XIX) is usually carried out in a chlorinated solvent such as methylene chloride at a temperature between −20° and +20° C.

The products of general formulae (III), (VIII), (XII), (XVI) and (XVII) can be prepared according to, or in a similar manner to, the methods described in the examples below, and especially according to:

G. G. Urquart et al., Org. Synth., 21, 36 (1941)

A. I. Vogel, J. Chem. Soc., 1822 (1948)

J. H. Chapman and L. N. Owen, J. Chem. Soc., 579 (1950)

H. R. Snyder et al., J. Am. Chem. Soc., 69, 2672 (1947)

D. D. Reynolds et al., J. Org. Chem., 26, 5125 (1961)

J. W. Haeffele et al., Proc. Sci. Toilet Goods Assoc., 32, 52 (1959)

H. Barrer et al., J. Org. Chem., 27 641 (1962)

J. H. Biel et al., J. Amer. Chem. Soc., 77, 2250 (1955)

when dealing with a product of general formula (III), (XII), (XVI) or (XVII) in which R, $R'_4$, $R''_4$ or $R'''_4$ denotes a substituted alkylthio or (heterocyclic ring radical)thio radical, or according to:

A. J. W. Headlee et al., J. Amer. Chem. Soc., 55, 1066 (1933)

B. K. Campbell and K. N. Campbell, J. Amer. Chem. Soc., 60, 1372 (1938)

R. C. Elderfield et al., J. Amer. Chem. Soc., 68, 1579 (1946)

when dealing with a product of general formula (XIV) or (XVII) in which $R''_4$ or $R'''_4$ denotes a substituted alkyloxy or (heterocyclic ring radical)oxy radical, or according to:

J. Amer. Chem. Soc., 54, 1499 (1932) and

J. Amer. Chem. Soc., 54, 3441 (1932),

when dealing with a product of general formula (VIII) or of general formula (III), (XVI) or (XVII) in which R, $R''_4$ or $R'''_4$ are substituted alkylamino radicals, or according to:

E. F. Elslager et al., J. Med. Chem., 17, 99 (1974)

L. M. Werbel et al., J. Het. Chem., 10, 363 (1973)

when dealing with a product of general formula (III), (XVI) or (XVII) in which R, $R''_4$ or $R'''_4$ are (heterocyclic ring radical)amino radicals.

It is to be understood that in the above methods, when R, $R_2$, $R_3$, $R'_4$, $R''_4$ or $R'''_4$ contain a secondary amine group capable of interfering with the reaction, this must first be protected by any known method which does not affect the remainder of the molecule. The protective radical is removed after reaction under the conditions described earlier.

Where applicable, the isomers of the products of general formula (I) and/or the products of general formula (V) can be separated by chromatography or by high performance liquid chromatography.

The products of general formula (V) can be purified as mentioned earlier for the products of general formula (I).

The pristinamycin $II_B$ derivatives of formula (I) and their pharmaceutically acceptable salts exhibit particularly advantageous antibacterial properties in vitro and in vivo.

In vitro, the products of formula (I) have shown themselves to be active towards *Staphylococcus aureus* Smith at concentrations from 4 to 100 $\mu g/cm^3$. In addition, they have a synergistic effect on the antibacterial action of pristinamycin $I_A$ in concentrations greater than 0.1 and 10 $\mu g/cm^3$.

In vivo, the products of formula (I) have shown themselves to be active in the mouse in experimental infections with *Staphylococcus aureus* Smith at dosages between 40 mg/kg and dosages greater than 300 mg/kg by the subcutaneous route. When they are combined with pristinamycin $I_A$ in proportions from 10–90% to 90–10%, they have a synergistic effect on the antimicrobial action at dosages between 8 and 200 mg/kg by the subcutaneous route.

The acute toxicity of the products of formula (I), expressed as their $LD_{50}$, is generally between 300 mg/kg and dosages greater than 1 g/kg by the subcutaneous route in the mouse.

The products of special interest are those of formula (I) in which the symbol R denotes:

either a nitrogen-containing 5 or 6-membered heterocyclic ring radical unsubstituted or substituted by an alkyl radical,

or an alkyl chain of 2 to 4 carbon atoms and substituted by 1 or 2 radicals chosen from phenyl, cycloalkylamino of 3 to 6 ring atoms, and N-alkyl-N-cycloalkylamino of 3 to 6 ring atoms, alkylamino, dialkylamino, dialkylcarbamoyloxy (the alkyl moieties of these two latter radicals being unjoined or joined to form, with the nitrogen atom to which they are attached, a saturated or unsaturated 5 or 6-membered heterocyclic ring which may contain another hetero atom chosen from nitrogen, oxygen and sulphur in the form of sulphoxide or sulphone, and unsubstituted or substituted by alkyl), or substituted by a nitrogen-containing 5 or 6-membered heterocyclic ring which may contain another hetero atom chosen from nitrogen, oxygen and sulphur in the form of sulphoxide or sulphone and unsubstituted or substituted by alkyl, this heterocyclic ring being linked to the alkyl by a carbon atom of the ring, it being understood that a least one of the substituents carried by the above alkyl chain is a nitrogen-containing substituent capable of forming salts, and n is 1 or 2; and, among these products, those which are especially active are the products of formula (I) in which R denotes an alkyl chain containing 2 to 4 carbon atoms substituted by 1 or 2 radicals chosen from phenyl, cycloalkylamino of 5 to 6 ring atoms, N-alkyl-N-cycloalkylamino of 5 or 6 ring atoms, alkylamino of 1 to 4 carbon atoms, and dialkylamino (in which the alkyl moieties contain 1 to 3 carbon atoms each or form, with the nitrogen atom to which they are attached, a saturated 5 or 6-membered heterocyclic ring), or R denotes a nitrogen-containing 5 or 6-membered heterocyclic ring unsubstituted or substituted by alkyl of 1 to 4 carbon atoms, at least one of the substituents carried by the alkyl chain being a nitrogen-containing substituent capable of forming salts, and at least one of the radicals carried by this chain is placed in a 1- or 2-position, and n is 1 or 2.

The following derivatives of pristinamycin $II_B$ of formula (I) are of especial interest.

26-(2-diethylamino-1-methylethyl)sulphinylpristinamycin $II_B$

26-[(2R)2-dimethylaminobutyl]sulphinylpristinamycin $II_B$

26-(2-diethylaminopropyl)sulphinylpristinamycin $II_B$

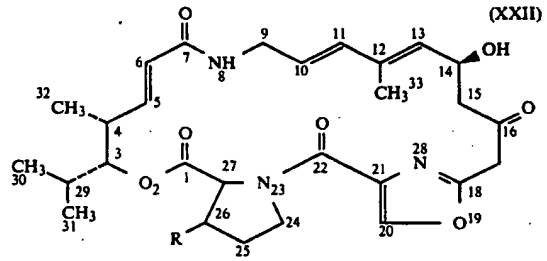
26-(2-diisopropylaminoethyl)sulphonylpristinamycin $II_B$.

For use in therapy, the compounds of formula (I) can be used as such, that is to say in the form of the base, in combination with already known synergistins, but, since the chief advantage of the products of the invention is their solubility in water, it is especially advantageous to use them in the form of pharmaceutically acceptable salts, in combination with known synergistins or with the synergistins of formula (V), dissolved either in the form of pharmaceutically acceptable salts or, where applicable, in the form of the base when the solubility is sufficient for the solution produced to contain (in a volume suitable for a single dose) a quantity of active ingredient which is at least equal to the therapeutically active dose.

Both for the products of formula (I) and for the products of formula (V), the pharmaceutically acceptable salts which can be mentioned are the salts of addition with inorganic acids such as hydrochlorides, hydrobromides, sulphates, nitrates, phosphates, or with organic acids, such as acetates, propionates, succinates, maleates, fumarates, methanesulphonates, p-toluenesulphonates, isethionates, or substitution derivatives of these compounds. There can also be mentioned, as pharmaceutically acceptable salts, the salts with alkali metals (such as sodium and potassium salts), with alkaline-earth metals (such as the magnesium salt), the ammonium salt and salts of addition with nitrogen-containing organic bases (ethanolamine, diethanolamine, trimethylamine, triethylamine, methylamine, propylamine, diisopropylamine, N,N-dimethylethanolamine, benzylamine, dibenzylamine, dicyclohexylbenzylamine, N-benzyl-β-phenethylamine, N,N'-dibenzylethylenediamine, benzhydrylamine, arginine, leucine, lysine or N-methylglucamine).

Quaternary ammonium salts corresponding to the anions listed above can be mentioned as pharmaceutically acceptable salts for the products of general formula (V) in which Z denotes a radical of general formula (VII) in which $R_4$ denotes a trialkylammonio radical.

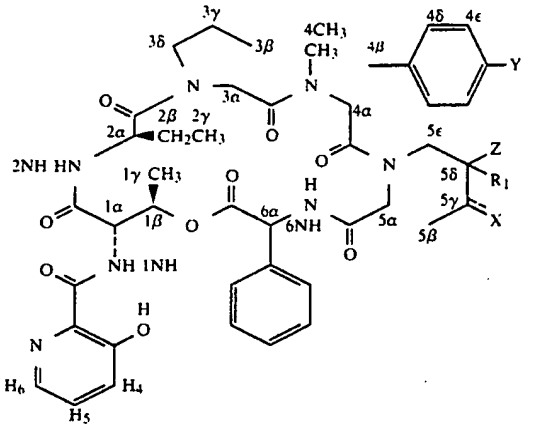
The following examples, given without implying any limitation, show how the invention can be put into practice. The NMR spectra of the products illustrated in these examples and in the reference examples which follow, show general characteristics which are common to all the products of general formula (I) or of general formula (V) and individual characteristics which are specific to each of the products, depending on the substituents. Only the individual characteristics due to the changeable radicals are mentioned in the examples or reference examples which follow. For the products of general formula (I), all the protons are designated according to the numbering indicated in the following formula:




For the synergistins of general formula (V) all the protons are designated according to the numbering indicated in the general formula (XXIII); this number-

ing is that recommended by J. O. Anteunis et al., [Eur. J. Biochem., 58, 259 (1975)].

(XXIII)



Unless stated otherwise, all the spectra were recorded at 250 MHz in deuterochloroform; the chemical shifts are expressed in ppm relative to the tetramethylsilane signal. The abbreviations used in the following text are as follows:

s=singlet
d=doublet
t=triplet
mt=multiplet
m=unresolved bands
dd=doublet of doublets
dt=doublet of triplets
ddd=doublet of doublets of doublets
dddd=doublet of doublets of doublets of doublets

It is to be understood that the various isomers have been classified arbitrarily according to the chemical shifts observed in NMR.

The names isomer $A_1$ and isomer $A_2$ of the products of general formula (I) in which n=1 are given to the isomers which have the characteristics: approximately 1.7 (s, $-CH_3$ at 33); approximately 3.8 (s, $>CH_2$ at 17); <5 (d, $-H_{27}$) isomer $A_2$ or >5 (d, $-H_{27}$) isomer $A_1$; approximately 5.50 (broad d, $-H_{13}$); approximately 6.20 (d, $-H_{11}$); approximately 6.6 (>NH at 8); >8 (s, $-H_{20}$).

The names isomer $B_1$ and isomer $B_2$ of the products of general formula (I) in which n=1 are given to the isomers which have the characteristics: approximately 1.5 (s, $-CH_3$ at 33); approximately 3.7 and 3.9 (2d, $>CH_2$ at 17); approximately 4.8 (mt, $-H_{13}$); <5 (d, $-H_{27}$) isomer $B_2$ or >5 (d, $-H_{27}$) isomer $B_1$; approximately 5.70 (borderline AB, $-H_{11}$ and $-H_{10}$); approximately 7.7 (>NH at 8); approximately 7.8 (s, $-H_{20}$).

The name isomer A of the product of general formula (II) is given to the isomer which has NMR characteristics identical to those listed above for the isomers $A_1$ and $A_2$ of the products of general formula (I), it being understood that the H at 27 is characterized by: 4.7 (d, $J \leqq 1$ Hz).

The name isomer B of the product of general formula (II) is given to the isomer which has NMR characteristics identical to those listed above for the isomers $B_1$ and $B_2$ of the products of general formula (I), it being understood that the H at 27 is characterized by: 4.6 (d, $J \leqq 2.5$ Hz).

In the following examples, the name "flash" chromatography is given to a purification technique in which a short chromatography column is used and operated under an intermediate pressure (50 kPa) with the use of a silica with a particle size distribution of 40–53 μm, according to W. C. Still, M. Kahn and A. Mitra (J. Org. Chem. 43, 2923 (1978).

In the examples described below, unless stated otherwise, all the products can be dissolved at a strength of at least 2%, in the form of hydrochloride.

## EXAMPLE 1

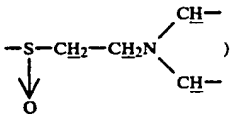
Trifluoroacetic acid (0.4 cc), and then 85% metachlorobenzoic acid (1.06 g) are added, under a nitrogen atmosphere; while the temperature is maintained at 0° C., to 26-(2-diisopropylaminoethyl)thiopristinamycin $II_B$ (isomer A) (3.59 g) dissolved in dichloromethane (40 cc) at 0° C. After 20 hours' stirring at 25° C., the reaction mixture is added to a saturated aqueous solution of sodium bicarbonate. The organic phase is separated off and then the aqueous phase is washed with methylene chloride (3×100 cc). The organic phase are combined, dried over magnesium sulphate, filtered and then concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. to give a yellow solid (4.2 g) which is purified by "flash" chromatography [(eluent: chloroform-methanol (90-10 by volume)], 20-cc fractions being collected. Fractions 22 to 28 are combined and concentrations to dryness under reduced pressure (2.7 kPa) at 30° C., to give a light-yellow solid, which is stirred in ethyl ether (10 cc). The solid obtained is separated off by filtration to give 26-(2-diisopropylaminoethyl)sulphinylpristinamycin $II_B$ (isomer $A_2$) (0.62 g) in the form of a yellow powder melting at about 155° C.

NMR spectrum:

0.90 to 1.15 [mt, $-CH_3$ at 32, 31, 30, $-N(CH-CH_3)_2$]

1.76 (s, $-CH_3$ at 33)

2.75 to 3.15 (mt, $>CH_2$ at 15, $-H_4$ and



3.81 (s, $>CH_2$ at 17)

4.76 (d, $-H_{27}$)

5.51 (d, $-H_{13}$)

6.20 (d, $-H_{11}$)

6.48 (m, >NH at 8)

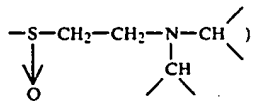
-continued
8.13 (S. $-H_{20}$)

Fractions 35 to 45 are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. to give a light-yellow solid which is stirred in ethyl ether (15 cc). The solid obtained is separated off by filtration to give 26-(2-diisopropylaminoethyl)sulphinylpristinamycin $II_B$ (80% isomer $A_1$, 20% isomer $A_2$) (1.07 g) in the form of a light-yellow powder melting at about 145° C.

NMR spectrum (isomer $A_1$):

1.72 (s, $-CH_3$ at 33)

2.70 to 3.15 (mt, $CH_2$ at 15, $-H_4$,



3.81 (s, $CH_2$ at 17)

5.26 (d, $-H_{27}$)

5.46 (d, $-H_{13}$)

6.15 (d, $-H_{11}$)

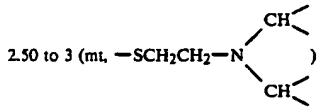
8.11 (s, $-H_{20}$)

26-(2-Diisopropylaminoethyl)thiopristinamycin $II_B$ can be prepared as follows:

2-Diisopropylaminoethanethiol (16 g) dissolved in dichloromethane (30 cc) is added dropwise under a nitrogen atmosphere to pristinamycin $II_A$ (52 g) dissolved in a mixture of dichloromethane (260 cc) and methanol (520 cc), at −30° C. The solution is stirred at −20° C. for 20 hours and then concentrated under reduced pressure (2.7 kPa) at 30° C. The solid obtained is stirred with ethyl ether (2×1000 cc), separated off by filtration and then crystallized from acetonitrile (100 cc). The crystals are separated off by filtration and then dried under reduced pressure (90 Pa) at 40° C. In this manner, 26-(2-diisopropylaminoethyl)thiopristinamycin $II_B$ (isomer A) (33.6 g) is obtained in the form of white crystals melting at about 122° C.

NMR spectrum:

1 to 1.15 (mt, isopropyl-$CH_3$)
1.72 (s, $-CH_3$ at 33)
1.80 to 2.20 (mt, $-H_{25}$, $-H_{29}$)



-continued

3.40 (broad d, $-H_{26}$)
4.74 (broad s, $-H_{27}$)
6.32 (m, $-NH_8$)
8.15 (s, $-H_{20}$)

2-Diisopropylaminoethanethiol can be prepared according to the method described by D. D. Reynolds, D. L. Fields and D. L. Johnson, J. Org. Chem. 26, 5125 (1961).

## EXAMPLE 2

Sodium bicarbonate (1.22 g) is added to 26-(2-diisopropylaminoethyl)thiopristinamycin $II_B$ (isomer A) (10 g) dissolved in chloroform (300 cc). The mixture is cooled to −50° C. and 98% meta-chloroperbenzoic acid (2.98 g) dissolved in chloroform (100 cc) is added dropwise. The mixture is stirred at −50° C. for 2 hours 15 minutes and then a saturated aqueous solution of sodium bicarbonate is added to it. After 15 minutes' stirring at 25° C., the mixture is separated and then the aqueous phase is washed with dichloromethane (3×200 cc). The organic phases are combined, dried over magnesium sulphate, filtered, and then concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. to give a whitish porous solid (10.62 g). The latter is dissolved in ethyl acetate (400 cc) and then treated with a 0.1N aqueous solution of hydrochloric acid (140 cc). The pH of the aqueous solution is then adjusted to 4.2 by adding a pH 4.2 buffer (400 cc). The aqueous phase is separated off and then the organic phase is washed with pH 4.2 buffer (400 cc). The aqueous phases are combined and washed with ethyl acetate (2×150 cc). After separation, the aqueous phase is adjusted to pH 7–8 adding sodium bicarbonate and is then washed with dichoromethane (3×300 cc). The organic phases are combined and then washed with pH 7.5 buffer (2×200 cc). The aqueous phase is washed with dichloromethane (50 cc) and then the organic phases are combined, dried over magnesium sulphate, filtered and concentrated to dryness under reduced pressure (2.7 kPa) at 30° C., to give a light-yellow solid (8.04 g), which is stirred in ethyl ether (100 cc), separated off by filtration and then dried under reduced pressure (90 Pa) at 40° C. In this manner, 26-(2-diisopropylaminoethyl)sulphinylpristinamycin $II_B$ (isomer $A_2$) (7.5 g) is obtained in the form of a yellow powder melting at about 158° C., the NMR characteristics of which are identical to those in Example 1.

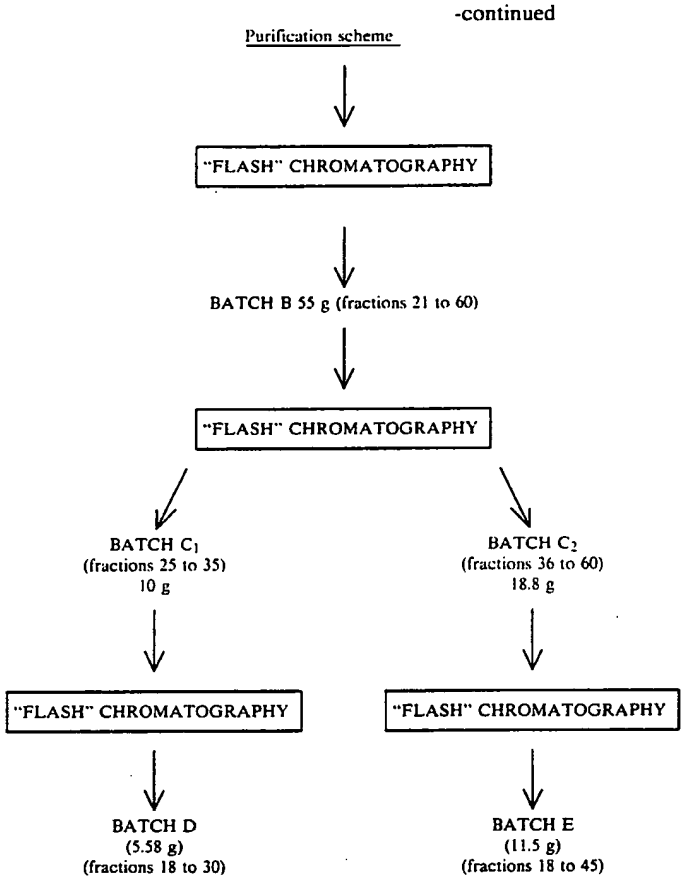
## EXAMPLE 3

The method used is that described in Example 1, but starting with 26-(2-diethylaminoethyl)thiopristinamycin $II_B$ (53.2 g), trifluoroacetic acid (6.25 cc) and meta-chloroperbenzoic acid (16.4 g). Three successive purifications by "flash" chromatography are carried out [eluent: chloroform-methanol (90–10 by volume)], 40-cc fractions being collected, according to the following scheme:

Purification scheme

BATCH A (68 g)

-continued




In all cases, the fractions recovered are concentrated to dryness under reduced pressure (2.7 kPa) at 30° C.

Batch D is stirred in ethyl ether (60 cc). The solid obtained is separated off by filtration. 26-(2-Diethylaminoethyl)sulphinylpristinamycin $II_B$ (isomer $A_2$) (5 g) is obtained in the form of a yellow powder melting at about 172° C.

NMR spectrum:

1.00 to 1.14 (mt, $-CH_3$ at 32 + chain $CH_3$)
1.75 (s, $-CH_3$ at 33)

2.55 to 3.20 (mt, $>CH_2$ at 15, $-H_4$, $-SCH_2CH_2N<$ (with $CH_2-$ and $CH_2-$), O)

3.82 (s, $>CH_2$ at 17)

4.81 (d, $-H_{27}$)
5.51 (d, $-H_{13}$)
6.19 (d, $-H_{11}$)

6.46 (dd, $>NH$ at 8)

8.13 (S, $-H_{20}$)

Batch E is stirred in ethyl ether (10 cc). The solid obtained is separated off by filtration. 26-(2-Diethylaminoethyl)sulphinylpristinamycin $II_B$ (60% isomer $A_2$), 15% isomer $A_1$, 12% isomer $B_1$, 13% isomer $B_2$) (10.9 g) is obtained.

NMR spectrum: 1.00 to 1.13 (mt, $-CH_3$ at 32 and $-N(CH_2CH_3)_2$ of $A_1$ and $A_2$), 1.54 (s, $-CH_3$ at 33 of $B_1$ and $B_2$), 1.68 (s, $-CH_3$ at 33 of $A_1$), 1.75 (s, $-CH_3$ at 33 of $A_2$), 2.65 to 2.95 (mt, $-S(O)CH_2CH_2N<$ and $H_4$ of $A_1$) 2.55 to 3.20 (mt, $>CH_2$ at 15, $-H_4$ and $-S(O)CH_2CH_2N<$ of $A_2$), 3.77 (borderline AB, $>CH_2$ at 17 of $A_1$), 3.82 (s, $>CH_2$ at 17 of $A_2$), 4.81 (d, $-H_{27}$ of $A_2$), 5.24 and 5.25 (2d, $-H_{27}$ of $A_1$ and of $B_1$), 5.41 (d, $-H_{13}$ of $A_1$), 5.51 (d, $-H_{13}$ of $A_2$), 5.99 and 6 (2d, $-H_6$ of $B_1$ and $-H_6$ of $B_2$), 6.11 (d, $-H_{11}$ of $A_1$), 6.19 (d, $-H_{11}$ of $A_2$), 6.46 (dd, $>NH$ at 8 of $A_2$), 6.79 (dd, $>NH$ at 8 of $A_1$), 7.82 (s, $-H_{20}$ of $B_1$ and $B_2$), 8.12 (s, $-H_{20}$ of $A_1$), 8.13 (s, $-H_{20}$ of $A_2$).

26-(2-Diethylaminoethyl)thiopristinamycin $II_B$ can be prepared as follows: A solution of diethylaminoethanethiol (3.7 g) in methylene chloride (15 cc) is added to a suspension of pristinamycin $II_A$ (13.1 g) in methanol (150 cc). The solution obtained is stirred at a temperature of about 20° C. for 18 hours and is then poured into distilled water (1500 cc); the mixture obtained is extracted 3 times with methylene chloride (1000 cc in total). The organic phases are combined, dried over magnesium sulphate, filtered and then concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. The residue obtained is purified by "flash" chromatography [eluent: chloroform-methanol (90–10 by volume)]; after

fractions 5 to 23 have been concentrated to dryness under reduced pressure (2.7 kPa) at 30° C., 26-(2-diethylaminoethyl)thiopristinamycin $II_B$ (12.4 g) is obtained in the form of a yellow powder melting at about 105° C.

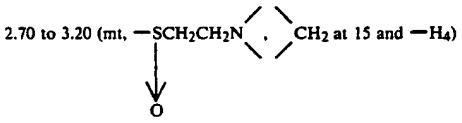
NMR spectrum: 1.05 (m, $-N(CH_2CH_3)_2+-H_{32}$), 1.70 (s, $-H_{33}$), 1.85 to 2.15 (m, $-H_{25}$, $-H_{29}$), 2.60 (q, $-N(CH_2CH_3)_2$), 2.75 (s, $-S-CH_2CH_2-$), 2.9 (dd, ABX system, $-H_{15}$), 3.10 (dd, ABX system, $-H_{15}$), 3.40 (ddd, $-H_{26}$), 3.80 (s, $-H_{17}$), 4.75 (d, $-H_{27}$), 5.50 (d, $-H_{13}$), 6.15 (d, $-H_{11}$), 6.60 (broad s, >NH at 8), 8.10 (s, $-H_{20}$).

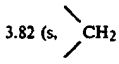
## EXAMPLE 4

By using a method similar to that described in Example 1, but starting from 26-(2-dimethylaminoethyl)thiopristinamycin $II_B$ (5.5 g), trifluoroacetic acid (0.67 cc) meta-chloroperbenzoic acid (1.8 g), and after a purification by "flash" chromatography [eluent: chloroform-methanol (90–10 by volume)], 30-cc fractions being collected, and concentrating fractions 23 to 40 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-(2-dimethylaminoethyl)sulphinylpristinamycin $II_B$ (70% isomer $A_2$, 15% isomer $A_1$, 7% isomer $B_1$, 8% isomer $B_2$) (0.4 g) is obtained in the form of a yellow powder melting at about 150° C.

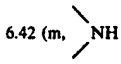
NMR spectrum (isomer $A_2$):

1.77 (s, $-CH_3$ at 33)
2.41 (s, $-N(CH_3)_2$)




4.84 (mt, $-H_3$ and $-H_{27}$)
5.52 (d, $-H_{13}$)
6.19 (d, $-H_{11}$)




8.14 (s, $-H_{20}$)

26-(2-Dimethylaminoethyl)thiopristinamycin $II_B$ can be prepared as follows:

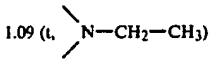
By using a mthod similar to that described in Example 3, but starting from pristinamycin $II_A$ (2.7 g) and 2-dimethylaminoethanethiol (0.58 g) and after purification by "flash" chromatography [eluent: chloroform-methanol (90–10 by volume)] and concentrating fractions 11 to 17 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-(2-dimethylaminoethyl)thiopristinamycin $II_B$ (1.1 g) is obtained in the form of a yellow powder melting at about 100° C.

NMR spectrum: 2.35 (s, 6H: $-N(CH_3)_2$), 2.80 (m, 4H: $-S-CH_2CH_2-N<$), 3.40 (ddd, 1H: $-H_{26}$), 4.75(d, 1H: $-H_{27}$), 8.10 (S, 1H: $-H_{20}$).

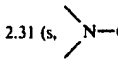
## EXAMPLE 5

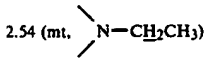
By using the same method as that described in Example 2, but startng from 26-(2-N-methyl-N-ethylaminoethyl)thiopristinamycin $II_B$ (90% isomer A 10% isomer B). (4.7 g), sodium bicarbonate (1.22 g), and 98% meta-chloroperbenzoic acid (1.41 g), and after purification by "flash" chromatography [eluent: dichloromethane-methanol (90–10 by volume)], 20-cc fractions being collected, and concentrating fractions 44 to 52 to dryness under reduced pressure (2.7 kPa) at 30° C., a yellow solid (2.47 g) is obtained, which is stirred in ethyl ether (50 cc), separated off by filtration and then dried under reduced pressure (90 Pa) at 40° C. In this manner, 2-(N-methyl-N-ethyl-2-aminoethyl)sulphinylpristinamycin $II_B$ (isomer $A_2$) (2.3 g) is obtained in the form of a yellow powder melting at about 145° C.

NMR spectrum

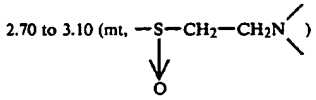


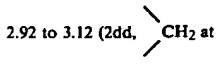

1.76 (s, $-CH_3$ at 33)



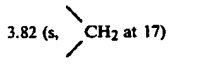




2.80 (mt, $-H_4$)

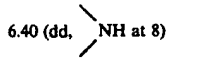



3.24 (mt, $-H_{26}$)




4.82 (s, $-H_{27}$)
5.51 (d, $-H_{13}$)




8.13 (S, $-H_{20}$)

26-(N-Methyl-N-ethyl-2-aminoethyl)thiopristinamycin $II_B$ (90% isomer A, 10% isomer B) can be prepared by using the same procedure as that described in Example 1, but starting from pristinamycin $II_A$ (14.11 g) and N-methyl-N-ethyl-2-aminoethanethiol (3.2 g). After stirring for 4 days at −20° C. and purification by "flash" chromatography [eluent: chloroform-methanol (90–10 by volume)], 80-cc fractions being collected, followed by concentration of fractions 25 to 48 to dryness under reduced pressure (2.7 kPa) at 30° C., a yel-

low solid (4.75 g) is obtained, which is dried under reduced pressure (90 kPa) at 40° C. In this manner, 26-(N-methyl-N-ethyl-2-aminoethyl)thiopristinamycin $II_B$ (90% isomer A, 10% isomer B) (4.7 g) is obtained in the form of a yellow powder melting at about 140° C.

NMR spectrum: 1.1 (mt, $CH_2\underline{CH_3}$), 1.73 (s, $CH_3$ at 33), 2.30 (s, $>N-CH_3$), 2.45 to 2.6 (mt, $>N-\underline{CH_2}CH_3$), 2.68 to 2.78 (2mt, $-S-CH_2-CH_2N<$), 2.78 (mt, $-H_4$), 2.90 and 3.12 (2dd, $-CH_2-$ at 15), 3.40 (d, $-H_{26}$), 3.83 (s, $-CH_2-$ at 17), 4.76 (s, $-H_{27}$), 5.48 (d, $-H_{13}$), 6.14 (d, $-H_{11}$), 6.34 (mf, >NH at 8), 8.11 (s, $-H_{20}$).

N-Methyl-N-ethyl-2-aminoethanethiol can be obtained by a method similar to that described by D. D. Reynolds et al., J. Org. Chem. 26, 5125 (1961), from N-methyl-N-ethylamine (25 g) and ethylene thiocarbonate (43.7 g). After distillation. N-methyl-N-ethyl-2-aminoethanethiol (1.3 g) is obtained in the form of a colourless liquid.

[B.p. (6.7 kPa)=52° C. ]

## EXAMPLE 6

Using a method similar to that described in Example 1, but starting from 26-(3-dimethylaminopropyl)thiopristinamycin $II_B$ (50:50 A/B isomers) (9.8 g), trifluoroacetic acid (1.18 cc) and meta-chloroperbenzoic acid (3.1 g) and after purification by "flash" chromatography [eluent: chloroform-methanol (80–20 by volume)], 15-cc fractions being collected, and concentrating fractions 53 to 75 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-(3-dimethylaminopropyl)sulphinylpristinamycin $II_B$ (mixed isomers) (1.6 g) is obtained in the form of a yellow powder melting at about 165° C.

NMR spectrum (mixture of isomers of type $A_2$≃45%, $B_2$≃35% and $B_1$≃15%): 1.53 (s, $-CH_3$ at 33 $B_2$ and $B_1$), 1.75 (s, $-CH_3$ at 33 of $A_2$), 2.26, 2.28 and 2.32 (3s, $>NCH_3$ of the 3 isomers), 3.82 (s, $>CH_2$ at 17 of $A_2$), 3.70 and 3.88 (2d, $>CH_2$ at 17 of $B_1$), 3.69 and 3.91 (2d, $>CH_2$ at 17 of $B_2$), 4.76 (d, $-H_{27}$ of $B_2$), 5.25 (d, $-H_{27}$ Of $B_1$), 5.50 (d, $-H_{13}$ of $A_2$), 7.63 (mt, >NH at 8 of $B_2$), 7.74 (mt, >NH at 8 of $B_1$), 7.82 (s, $-H_{20}$ of $B_2$ and $B_1$), 8.14 (s, $-H_{20}$ of $A_2$). 26-(3-Dimethylaminopropyl)thiopristinamycin $II_B$ can be obtained as follows:

By using a method similar to that described in Example 3, but starting from pristinamycin $II_A$ (5.25 g) and 3-dimethyl-aminopropanethiol (1.3 g), and after purification by "flash" chromatography [eluent: chloroform-methanol (90–10 by volume)] and concentrating fractions 6 to 29 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-(3-dimethylaminopropyl)thiopristinamycin $II_B$ (3.3 g) is obtained in the form of a yellow powder melting at about 100° C.

NMR spectrum:

1.50 (s, 3H × 0.5: $-H_{33}$ 1st isomer)
1.70 (s, 3H × 0.5: $-H_{33}$ 2nd isomer)

1.80 (m, 2H: $-SCH_2-\underline{CH_2}-CH_2N<$)

2.20 (s, 6H × 0.5: $-N(CH_3)_2$ 1st isomer)
2.25 (s, 6H × 0.5: $-N(CH_3)_2$ 2nd isomer)

2.40 (m, 2H: $-S\underline{CH_2}-CH_2-CH_2N<$)

2.70 (m, 2H: $-SCH_2-CH_2-\underline{CH_2}N<$)

3.35, 3.45 (2m, 1H: $-H_{26}$ of each isomer)

4.60, 4.70 (2d, 1H: $-H_{27}$ of each isomer)

7.80, 8.10 (2s, 1H: $-H_{20}$ of each isomer)

## EXAMPLE 7

By using a method similar to that described in Example 1, but starting from 26-(2-diethylaminopropyl)thiopristinamycin $II_B$ (6.3 g), trifluoroacetic acid (0.72 cc) and meta-chloroperbenzoic acid (1.91 g), and after purification by "flash" chromatography [eluent: chloroform-methanol (90–10 volume)], 60-cc fractions being collected, and after concentrating fractions 7 to 9 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-(2-diethylaminopropyl)sulphinylpristinamycin $II_B$ (isomers $A_2$) (0.99 g) is obtained in the form of a yellow powder melting at about 150° C.

NMR spectrum: 1.03 to 1.20 (mt, $-CH_2-CH(\underline{CH_3})N(CH_2\underline{CH_3})_2$), $CH_3$ at 32), 1.76 (s, $-CH_3$ at 33), 3.82 (s, $CH_2$ at 17), 4.79 (m, $-H_{27}$), 5.53 (d, $-H_{13}$), 6.20 (d, $-H_{11}$), 6.42 (m, >NH at 8), 8.13 (s, $-H_{20}$).

After concentrating fractions 23 to 35 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-(2-diethylaminopropyl)sulphinylpristinamycin $II_B$ (isomers $A_1$) (0.64 g) is obtained in the form of a beige-yellow powder melting at about 160°–170° C.

NMR spectrum:

1.14 (mt, $-N(CH_2\underline{CH_3})_2$)

1.24 (broad d, $\underline{CH_3}-CH-N<$)

1.73 (s, $-CH_3$ at 33)

3.81 (borderline AB, $>CH_2$ at 17)

5.28 (d, $-H_{27}$)
5.43 (d, $-H_{13}$)
6.15 (d, $-H_{11}$)

6.88 (m, >NH at 8)

8.10 (s, $-H_{20}$)

26-(2-Diethylaminopropyl)thiopristinamycin $II_B$ can be prepared as follows:

By using a method similar to that described in Example 3, but starting from pristinamycin $II_A$ (3.15 g) and 2-diethylaminopropanethiol (1.8 g), and after purification by "flash" chromatography [eluent: methylene

chloride-methanol (90–10 by volume)], 20-cc fractions being collected, and concentrating fractions 3 to 5 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-(2-diethylaminopropyl)thiopristinamycin $II_B$ (1.4 g) is obtained in the form of a yellow powder melting at about 160° C.

NMR spectrum:

1 (m, 9H: $-H_{32}$ + $-N(CH_2\underline{CH_3})_2$)

2.50 (m, 6H: $-S-C\underline{H_2}-\underset{|}{CH}-N(C\underline{H_2}CH_3)_2$)

3.30 (m, 1H: $-H_{26}$)
4.70 (d, 1H: $-H_{27}$)
8.12 (s, 1H: $-H_{20}$)

2-(Diethylaminopropanethiol can be prepared as follows:

A 10N aqueous solution of sodium hydroxide (25 cc) is added to a solution of 3-S-isothioureido-2-diethylaminopropane dihydrochloride (29.5 g) in distilled water (150 cc). The mixture is heated to 100° C. for 1 hour, cooled to 20° C., adjusted to pH 9 by adding a 12N aqueous solution of hydrochloric acid (8 cc), and is then extracted with ethyl ether (3×100 cc). The ether phases are combined, dried over potassium carbonate, filtered and then concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. The mixture is purified by distillation. 2-Diethylamino-1-propanethiol (5.8 g) is obtained in the form of a colourless liquid. [B.p. (2.7 kPa)=78° C.]

1-S-Isothioureido-2-diethylaminopropane dihydrochloride can be prepared as follows:

Thiourea (16.7 g) is added to a solution of 1-chloro-2-diethylaminopropane hydrochloride (41 g) in dimethylformamide (200 cc). The mixture is heated to 100° C. for 30 minutes, and then cooled to 20° C. The white precipitate formed is collected by filtration, washed with dimethylformamide (3×20 cc) and then with ethyl ether (3×20 cc). 1-S-Isothioureido-2-diethylaminopropane dihydrochloride (29.6 g) is obtained in the form of white crystals melting at 247°–249° C.

1-Chloro-2-diethylaminopropane hydrochloride can be obtained as follows:

2-Diethylaminopropanol hydrochloride (45.2 g) is added over 15 minutes to thionyl chloride (100 cc) and the mixture is heated to 80° C. After 2 hours' stirring, excess thionyl chloride is distilled off and the residue is taken up with ethyl ether (200 cc). 1-Chloro-2-diethylaminopropane hydrochloride crystallizes out. After filtration, white crystals (48.2 g) melting at 112° C. are obtained.

2-Diethylaminopropanol hydrochloride can be obtained as follows:

A solution of ethyl 2-diethylaminopropionate (66 g) in ethyl ether (330 cc) is added slowly at 20° C. to a suspension of lithium aluminium hydride (10.6 g) in ethyl ether (1 liter) kept under nitrogen. The reaction is maintained for 5 hours at a temperature of 35° C., and the temperature is then lowered to 0° C. Water (12.4 cc), a 5N aqueous solution of sodium hydroxide (9.1 cc) and then water (41.3 cc) are then added dropwise at 0° C., the mixture is stirred for 30 minutes and is then filtered through sintered glass and is then washed with ethyl ether. The ether phase is dried over potassium carbonate, filtered and then concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. A yellow liquid (43.8 g) is obtained and is dissolved in acetone (200 cc), to which a 4.5N solution (78 cc) of hydrogen chloride gas in ethyl ether is then added. 2-Diethylaminopropanol hydrochloride crystallizes out. After filtration, white crystals (45.2 g) melting at 97°–100° C. are obtained.

Ethyl 2-diethylaminopropionate can be obtained according to Braun et al., Beilstein, 61, 1425 (1928).

## EXAMPLE 8

The method used is similar to that described in Example 2, but starting from 26-(2-diethylaminopropyl)thiopristinamycin $II_B$ (isomers A) (4 g), 98% metachloroperbenzoic acid (1.16 g) and solid sodium bicarbonate (1 g). After purification by "flash" chromatography [eluent: chloroform-methanol (93-7) by volume)] and concentrating fractions 21 to 48 to dryness under reduced pressure (2.7 kPa) at 30° C., 25-cc fractions being collected, 26-(2-diethylaminopropyl)sulphinylpristinamycin $II_B$ (isomers $A_2$) (2.69 g) is obtained in the form of a yellow powder which has characteristics identical to those of the product obtained in Example 7.

26-(2-Diethylaminopropyl)thiopristinamycin $II_B$ (isomer A) can be obtained by using a method similar to that described in Example 1, but starting from pristinamycin $II_A$ (15 g) and 2-diethylaminopropanethiol (4.62 g). After purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)] and concentrating fractions 27 to 52 to dryness under reduced pressure (2.7 kPa) at 30° C., 40-cc fractions being collected, a yellow solid (12 g) is obtained and stirred in ethyl ether (60 cc), filtered off and then dried. 26-(2-Diethylaminopropyl)thiopristinamycin $II_B$ (isomer A) (8.2 g) is obtained in the form of a light-yellow powder melting at about 122° C.

NMR spectrum:

1 to 1.15 (mt, ethyl-$C\underline{H_3}$ + $CH_3-\underset{|}{CH}-N(C_2H_5)_2$)

1.70 (s, $-CH_3$ at 33)

2.35 to 2.60 (mt, $-N(C\underline{H_2}-CH_3)_2$)

2.50 to 3.10 (mt, $-SCH_2\underset{|}{CH}-$)

2.75 (mt, $-H_4$)

2.89 and 3.05 (2dd), 2.92 and 3.08 (2dd) $\rangle CH_2$ at 15)

3.30 (mt), 3.37 (mt) $-H_{26}$)

3.80 (s, $CH_2$ at 17)

4.69 (d), 4.71 (d) $-H_{27}$)

-continued

5.45 (d, $-H_{13}$)

6.13 (d) 6.14 (d) $-H_{11}$)

6.4 to 6.60 (mt, >NH at 8)

6.51 (dd) 6.53 (dd) $-H_5$)

8.09 (S, $-H_{20}$)

2-Diethylaminopropanethiol can be obtained as described earlier in Example 7.

## EXAMPLE 9

The method used is similar to that described in Example 2 but starting from 26-(1-diethylamino-2-propyl)-thiopristinamycin $II_B$ (isomers A) (4.58 g), 98% metachloroperbenzoic acid (1.29 g) and solid sodium bicarbonate (1.14 g). After purification by "flash" chromatography [eluent: chloroform-methanol (97-3 by volume)], 20-cc fractions being collected, and concentrating, respectively, fractions 59 to 77 and fractions 79 to 97 under reduced pressure (2.7 kPa) at 30° C., there are obtained: from fractions 79 to 97, 26-(1-diethylamino-2-propyl)sulphinylpristinamycin $II_B$ (first isomer) (1.47 g) in the form of a light-yellow solid melting at about 132° C.

NMR spectrum:

1.02 (t, ethyl-$CH_3$)

1.34 (d, $CH_3-CH(-CH_2N(C_2H_5)_2)$)

1.72 (s, $-CH_3$ at 33)

2.5 to 2.7 (mt, $-CH_2-N(-CH_2-)(-CH_2-)$)

2.77 (mt, $-H_4$)

2.87 and 3.09 (2dd, $CH_2$ at 15)

2.97 (mt, $-S(=O)-CH$)

3.72 (mt, $-H_{26}$)

3.80 (s, CH at 17)

4.92 (mt, $-H_{27}$)
5.43 (d, $-H_{13}$)
6.15 (d, $-H_{11}$)

6.72 (dd, NH at 8)

8.06 (s, $-H_{20}$)

and from fractions 59 to 77, 26-(1-diethylamino-2-propyl)sulphinylpristinamycin $II_B$ (second isomer) (1.07 g) in the form of a light-yellow solid melting at about 128° C.

NMR spectrum: 1.72 (s, $CH_3$ at 33), 3.4 (mt, $-H_{26}$), 3.79 (s, $CH_2$ at 17), 4.74 (mt, $-H_{27}$), 5.48 (d, $-H_{13}$), 6.18 (d, $-H_{11}$), 6.80 (mf, >NH at 8), 8.09 (s, $-H_{20}$).

26-(1-Diethylamino-2-propyl)thiopristinamycin $II_B$ (isomers A) can be obtained by using a method similar to that described in Example 1 but starting from pristinamycin $II_A$ (13 g) and 1-diethylamino-2-propanethiol (4 g). After purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)] and concentrating fractions 46 to 55 to dryness under reduced pressure (2.7 kPa) at 30° C., 50-cc fractions being collected, a pale yellow solid (8 g) is obtained and recrystallized from acetonitrile (30 cc). After filtration and drying, 26-(2-diethylamino-2-propyl)thiopristinamycin $II_B$ (isomers A) (5.91 g) is obtained in the form of white crystals melting at 136° C.

NMR spectrum:

0.9 to 1.10 (mt, $-N(CH_2CH_3)_2$)

1.33 to 1.37 (2d, $CH_3-CH(-CH_2N<)$)

1.7 (s, $-CH_3$ at 33)

2.4 to 2.65 (mt, $-CH_2N(CH_2-)(CH_2-)$)

2.76 (mt, $-H_4$)

3 (mt, $-S-CH<$)

2.9 and 3.1 (2dd, $CH_2$ at 15)

3.52 (mt, $-H_{26}$)

3.81 (s, $CH_2$ at 17)

4.78 (mt, $-H_{27}$)
5.46 (d, $-H_{13}$)
6.14 (d, $-H_{11}$)

6.40 (mt, NH at 8)

-continued

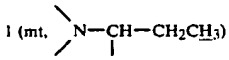
8.09 and 8.10 (2s, $-H_{20}$)

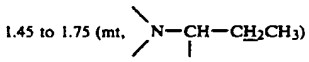
1-Diethylamino-2-propanethiol can be obtained according to the method described by R. T. Wragg, J. Chem. Soc. (C), 2087 (1969).

## EXAMPLE 10

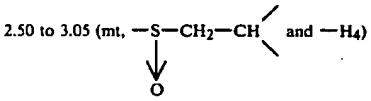
A method similar to that described in Example 2 is used, but starting from 26-[(2R)-2-dimethylaminobutyl]-thiopristinamycin $II_B$ (isomer A) (1.7 g), sodium bicarbonate (0.50 g) and 98% meta-chloroperbenzoic acid (0.45 g). After purification by "flash" chromatography [eluent: ethyl actate-methanol (85–15 by volume)] and concentrating fractions 35 to 58 to dryness under reduced pressure (2.7 kPa) at 30° C., a white solid (1.1 g) is obtained which is stirred in ethyl ether (30 cc). After filtration and drying, 26-[(2R)-2-dimethylaminobutyl]-sulphinylpristinamycin $II_B$ (isomer $A_2$) (0.95 g) is obtained in the form of a white solid melting at about 126° C.

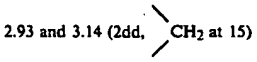
NMR spectrum:



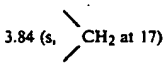




1.78 (s, $-CH_3$ at 33)

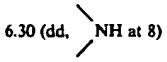



3.31 (mt, $-H_{26}$)




4.84 (d, $-H_{27}$)
5.51 (d, $-H_{13}$)
6.19 (d, $-H_{11}$)

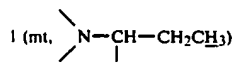


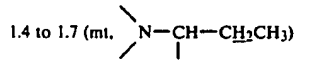

8.15 (s, $-H_{20}$)

26-[(2R)-2-Dimethylaminobutyl]thiopristinamycin $II_B$ (isomer A) can be obtained by using a method similar to that described in Example 1 but starting from pristinamycin $II_A$ (8 g) and (2R)-2-dimethylaminobutanethiol. After purification by "flash" chromatography [eluent: dichloromethane-methanol (90-10 by volume)] and concentrating fractions 36 to 55 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-[(2R)-2-dimethylaminobutyl]thiopristinamycin $II_B$ (isomer A) (3 g) is obtained in the form of a light-yellow solid melting at about 120° C.

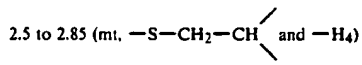
Crystallization of this product (0.9 g) from acetonitrile (5 cc) produces, after separation by filtration, 26-[(2R)-2-dimethylaminobutyl]thiopristinamycin $II_B$ (isomer A) (0.2 g) in the form of white crystals melting at 122° C.

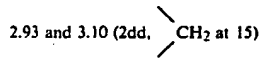
NMR spectrum:



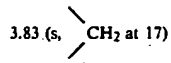




1.72 (s, $-CH_3$ at 33)
2.30 (s, $-N(CH_3)_2$)

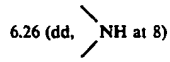



3.34 (broad d, $-H_{26}$)




4.76 (broad s, $-H_{27}$)
5.48 (d, $-H_{13}$)
6.14 (d, $-H_{11}$)




8.13 (s, $-H_{20}$)

(R)-2-Dimethylaminobutanethiol can be obtained using a method similar to that described below in Example 11, starting from triphenylphosphine (52.4 g), diisopropyl azodicarboxylate (40 cc), (R)-2-dimethylaminobutanol (12 g) and thiolacetic acid (15.2 cc) (in this case, the intermediate thioester is hydrolysed directly during the chromatography on silica gel).

After purification by "flash" chromatography [eluent: dichloromethane: 1000 cc, then dichloromethane-methanol (85-15 by volume): 2000 cc, then dichloromethane-methanol (80-20 by volume): 4000 cc], 100-cc fractions being collected, and concentrating fractions 42 to 60 to dryness under reduced pressure, a yellow oil (14 g) is obtained, which is purified by distillation. In this manner, (R)-2-dimethylaminobutanethiol (2.4 g) is obtained in the form of a colourless liquid. [B.p. (4 kPa)=70°-75° C.].

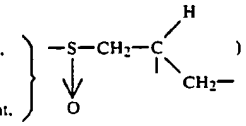
(R)-2-Dimethylamino-1-butanol can be obtained by a method identical to that described by M. Wenghoefer et al., J. Heterocycl. Chem., 7(6), 1407 (1970).

## EXAMPLE 11

26-[(2S)-2-Dimethylamino-3-phenylpropyl]thiopristinamycin $II_B$ (isomer A) (2.67 g), sodium bicarbonate (0.7 g) and 98% meta-chloroperbenzoic acid (0.7 g), after purification by "flash" chromatograhy [eluent: chloroform-methanol (90-10 by volume)], 20-cc fractions being collected, and concentrating fractions 19 to 23 to dryness under reduced pressure (2.7 kPa) at 30° C., a light-yellow solid (1.3 g) is obtained, which is stirred in ethyl ether (50 cc), and separated off by filtration to give 26-[(2S)-2-dimethylamino-3-phenylpropyl]sulphinylpristinamycin $II_B$ (isomer $A_2$) (1.18 g) in the form of a light-yellow solid melting at about 150° C.

NMR spectrum (400 MHz, $CDCl_3$)

1.73 (s, $-CH_3$ at 33)

2.4 to 2.6 (mt, 
2.8 to 3.15 (mt,

2.44 (s, $-N(CH_3)_2$)
2.77 (mt, $-H_4$)

2.89 and 3.1 (2dd,  at 15)

3.18 (mt, $-H_{26}$)

3.82 (s,  at 17)

4.68 (d, $-H_{27}$)
5.51 (d, $-H_{13}$)
6.19 (d, $-H_{11}$)

6.50 (dd,  at 8)

7.18 (d, phenyl ortho-H)
7.23 (t, phenyl para-H)
7.31 (t, phenyl meta-H)
8.13 (s, $-H_{20}$)

An aqueous solution containing 1% of 26-[(2S)-2-dimethylamino-3-phenylpropyl]sulphinylpristinamycin $II_B$ (isomer $A_2$) is obtained with:

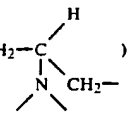
| | |
|---|---|
| product | 30 mg |
| 0.1 N hydrochloric acid | 0.45 cc |
| distilled water q.s. | 3 cc |

26-[(2S)-2-Dimethylamino-3-phenylpropyl]thiopristinamycin $II_B$ (isomer A) can be prepared by using a method similar to that described in Example 1 for the preparation of the starting material, but starting from pristinamycin $II_A$ (7.13 g) and (S)-2-dimethylamino-3-phenylpropanethiol (2.65 g) and after purification by "flash" chromatography [eluent: ethyl acetate-methanol (80-20) by volume)], 60-cc fractions being collected, and concentrating fractions 33 to 43 to dryness under reduced pressure (2.7 kPa) at 30° C., a light-yellow solid (4.6 g) is obtained which is stirred in ethyl ether (50 cc), filtered off and then dried under reduced pressure (90 Pa) at 45° C. In this manner, 26-[(2S)-2-dimethylamino-3-phenylpropane]thiopristinamycin $II_B$ (isomer A) (3.6 g) is obtained in the form of a pale yellow power melting at about 110° C.

NMR spectrum:

1.69 (s, $-CH_3$ at 33)

2.38 (s, $-N(CH_3)_2$)

2.35 to 3.05 (mt, 
)

2.73 (mt, $-H_4$)

2.89 and 3.10 (2dd,  at 15)

3.26 (broad d, $-H_{26}$)

3.81 (s,  at 17)

4.68 (broad s, $-H_{27}$)

5.47 (d, $-H_{13}$)

6.12 (d, $-H_{11}$)

6.27 (mf,  at 8)

7.18 (d, phenyl ortho-H)

7.21 (t, phenyl para-H)

7.30 (t, phenyl meta-H)

8.11 (s, $-H_{20}$)

(S)-2-Dimethylamino-3-phenylpropanethiol can be prepared as follows:

Sodium methoxide (0.2 g) is added under a nitrogen atmosphere to (S)-2-dimethylamino-3-phenylpropanethiolacetate (20 g: crude) dissolved in methanol (50 cc) and the mixture is heated under reflux for 2 hours. The mixture is then concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. to give a liquid which is purified by distillation. (S)-2-Dimethylamino-3-phenylpropanethiol (2.4 g) is obtained in the form of a colourless liquid [b.p. (14 Pa)=95° C.] which is used as such in the reaction which follows.

(S)-2-Dimethylamino-3-phenylpropanethiolacetate can be prepared as follows:

Triphenylphosphine (41.97 g) and tetrahydrofuran (310 cc) are added at 0° C. under a nitrogen atmosphere, and then diisopropyl azodicarboxylate (31.5 cc) is added dropwise and the mixture is left stirred for half an hour at 0° C. A mixture of (S)-2-dimethylamino-3-phenylpropanol (15 g) and of thiolacetic acid (11.44 cc) dissolved in tetrahydrofuran (160 cc) is added dropwise to the white suspension obtained. After being stirred for 1 hour at 0° C. and then for 1 hour 30 minutes at 25° C.,

the mixture is concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. Methanol (190 cc) is added to the oil obtained, the white solid which precipitates is removed by filtration, and the filtrate is concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. The residue is then stirred with isopropyl ether (200 cc), the white solid precipitated is again removed by filtration and the filtrate is concentrated to give a yellow oil (45 g), which is purified by "flash" chromatography [eluent: dichloromethane-methanol (90-10 by volume)], 100-cc fractions being collected. After concentrating fractions 37 to 55 to dryness under reduced pressure (2.7 kPa) at 30° C., (S)-2-dimethylamino-3-phenylpropanethiolacetate (10.4 g) is obtained in the form of an orange-yellow oil (containing triphenylphosphine oxide).

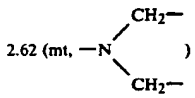
(S)-2-Dimethylamino-3-phenylpropanol can be prepared by using a method similar to that described by T. Hayashi et al., J. Org. Chem., 48, 2195 (1983).

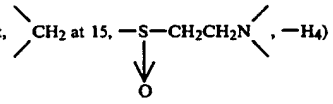
## EXAMPLE 12

By using a method similar to that described in Example 1, but starting from 26-[2-(1-pyrrolidinyl)ethyl]thiopristinamycin $II_B$ (90% isomer A), trifluoroacetic acid (1.47 cc), and meta-chloroperbenzoic acid (3.86 g), and after purification by "flash" chromatography [eluent: chloroform-methanol (85-15 by volume)], 30-cc fractions being collected, and concentrating fractions 18 to 25 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-[2-(1-pyrrolidinyl)ethyl]sulphinylpristinamycin $II_B$ (isomers: 60% $A_1$, 25% $A_2$, 15% $B_1$) (3.9 g) is obtained in the form of a yellow power melting at about 175° C.

NMR spectrum (isomer $A_1$):

1.74 (s, $-CH_3$ at 33)

2.62 (mt,  )

2.70 to 3.20 (mt,  )

3.81 (s,  )

5.28 (broad s, $-H_{27}$)
5.45 (d, $-H_{13}$)
6.14 (d, $-H_{11}$)

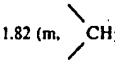
6.58 (mt,  )

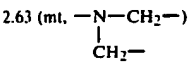
8.12 (s, $-H_{20}$)

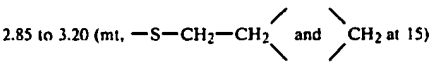
After concentrating fractions 26 to 43 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-[2-(1-pyrrolidinyl)ethyl]sulphinylpristinamycin $II_B$ (75% isomer $A_2$, 5% isomer $A_1$, 10% isomer $B_1$, 10% isomer $B_2$) (4.36 g) is obtained in the form of a yellow powder melting at about 145° C.

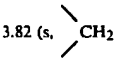
NMR spectrum (isomer $A_2$):

1.76 (s, $-CH_3$ at 33)

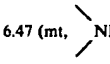
1.82 (m,  )

2.63 (mt,  )

2.85 to 3.20 (mt,  )

3.82 (s,  )

4.84 (dd, $-H_3$ + d, $-H_{27}$)
5.51 (d, $-H_{13}$)
6.18 (d, $-H_{11}$)

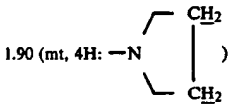
6.47 (mt,  )

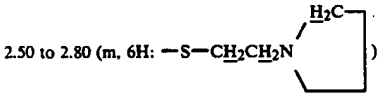
8.13 (s, $-H_{20}$)

26-[2-(1-Pyrrolidinyl)ethyl]thiopristinamycin $II_B$ can be prepared as follows:

By using a method similar to that described in Example 3 but starting from pristinamycin $II_A$ (5.25 g) and 2-(1-pyrrolidinyl)ethanethiol (1.7 g), and after purification by "flash" chromatography [eluent: chloroform-methanol (95-5by volume)] of 2-(1-pyrrolidnyl)ethanethiol, and after purification by "flash" chromatography [eluent: chloroform-methanol (95-5 by volume)] and concentrating fractions 19 to 60 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-[2-(1-pyrrolidinyl)ethyl]thiopristinamycin $II_B$ (3.9 g) is obtained in the form of a yellow powder melting at about 115° C.

NMR spectrum:

1.90 (mt, 4H:  )

2.50 to 2.80 (m, 6H:  )

3.40 (d, 1H: $-H_{26}$)
4.75 (d, 1H: $-H_{27}$)
8.10 (s, 1H, $-H_{20}$)

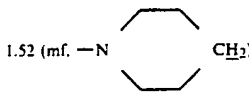
2-(1-Pyrrolidnyl)ethanethiol can be prepared according to the method described by J. W. Haeffele and R. W. Broge, Proc. Sci. Toilet Goods Assoc. 32, 52 (1959) [Chem. Abstr. 54, 17234e (1960)].

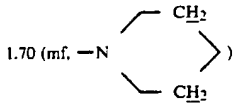
## EXAMPLE 13

By using a method similar to that described in Example 1, but starting from 26-(2-piperidinoethyl)thiopris-

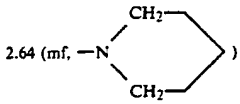
tinamycin $II_B$ (isomer A) (6 g), trifluoroacetic acid (0.69 cc) and 85% meta-chloroperbenzoic acid (1.82 g), after purification by "flash" chromatography [eluent: chloroform-methanol (85-15 by volume)], 20-cc fractions being collected and concentrating fractions 52 to 105 to dryness under reduced pressure (2.7 kPa) at 30° C., a yellow solid (4.7 g) is obtained, which is again purified by "flash" chromatography [eluent: chloroform-methanol (85-15 by volume)], 5-cc fractions being collected. After concentrating fractions 92 to 99 under reduced pressure (2.7 kPa) at 30° C., a yellow solid (1.83 g) is obtained, which is stirred in ethyl ether (20 cc), separated off by filtration, and then dried under reduced pressure (90 Pa) at 30° C. In this manner, 26-(2-piperidinoethyl)thiopristinamycin $II_B$ (isomers: 90% $A_2$, 10% $A_1$) (1.51 g) is obtained in the form of a yellow powder melting at about 162° C.

NMR spectrum (400 MHz, $CDCl_3$)

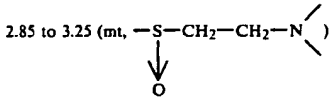


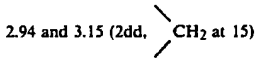




1.78 (s, $-CH_3$ at 33)

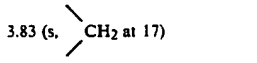



2.80 (mt, $-H_4$)

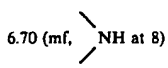



3.20 (mt, $-H_{26}$)




4.92 (d, $-H_{27}$)
5.54 (d, $-H_{13}$)
6.24 (d, $-H_{11}$)




8.14 (s, $-H_{20}$)

After concentrating fractions 100 to 140 to dryness under reduced pressure (2.7 kPa) at 30° C., a yellow solid (2.11 g) is obtained, which is stirred in ethyl ether (20 cc), separated off by filtration and then dried under reduced pressure (90 Pa) at 30° C. 26-(2-Piperidinoethyl)thiopristinamycin $II_B$ (isomers: 50% $A_1$, 50% $A_2$) (1.75 g) is obtained in the form of a yellow powder melting at about 152° C.

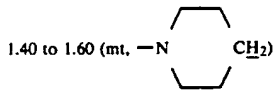
NMR spectrum (400 MHz, $CDCl_3$), 1.74 (s, $-CH_3$ at 33 isomer $A_1$), 1.78 (s, $-CH_3$ at 33 isomer $A_2$), 3.20 (mt, $-H_{26}$ isomer $A_2$), 3.46 (mt, $-H_{26}$ isomer $A_1$), 3.82 (borderline AB, $>CH_2$ at 17 isomer $A_1$), 3.83 (s, $>CH_2$ at 17 isomer $A_2$), 4.90 (d, $-H_{27}$ isomer $A_2$), 5.30 (s, $-H_{27}$ isomer $A_1$), 5.52 (d, $-H_{13}$ isomer $A_1$), 5.54 (d, $-H_{13}$ isomer $A_2$), 6.60 (dd, $-H_5$ isomer $A_2$), 6.70 (dd, $-H_5$ isomer $A_1$). 8.14 (s, $-H_{20}$, isomers $A_2$ and $A_1$)

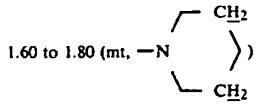
26-(2-Piperidinoethyl)thiopristinamycin $II_B$ (isomer A) can be obtained as follows:

By using a method similar to that described in Example 1, but starting from pristinamycin $II_A$ (11.8 g) and 2-piperidinoethanethiol (3.58 g), and after purification by "flash" chromatography [eluent: chloroform-methanol (85-15 by volume)], 60-cc fractions being collected, and concentrating fractions 24 to 31 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-(2-piperidinoethyl)thiopristinamycin $II_B$ (isomer A) (8.3 g) is obtained in the form of a light-yellow powder melting at about 120° C.

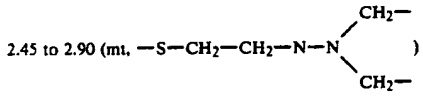
NMR spectrum:

1.08 (d, $-CH_3$ at 32)

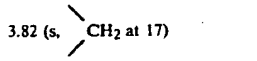



1.73 (s, $-CH_3$ at 33)




3.43 (mt, $-H_{26}$)




4.71 (broad s, $-H_{27}$)
5.50 (d, $-H_{13}$)
8.13 (s, $-H_{20}$)

2-Piperidinoethanethiol can be obtained by a method identical to that described by D. D. Reynolds, D. L. Fields and D. J. Johnson, J. Org. Chem., 26, 5125 (1961).

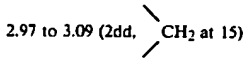
## EXAMPLE 14

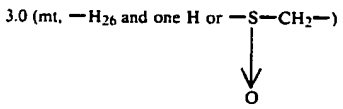
By using a method similar to that described in Example 2, but starting from 26-[2-(1-imidazolyl)ethyl]thiopristinamycin $II_B$ (isomers: 85% A, 15% B) (3.2 g), sodium bicarbonate (1 g) and 98% meta-chloroperbenzoic acid (0.93 g), after purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)], 25-cc fractions being collected, and concentrating fractions 29 to 49 to dryness under reduced pressure

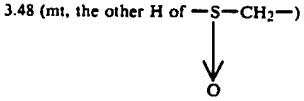
(2.7 kPa) at 30° C., a yellow solid (1.4 g) is obtained. The solid obtained is purified again by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)], 10-cc fractions being collected. After concentrating fractions 47 to 55 to dryness under reduced pressure (2.7 kPa) at 30° C., a light-yellow solid (0.62 g) is obtained, which is stirred in ethyl ether (20 cc), separated off by filtration and then dried under reduced pressure (90 Pa) at 40° C. In this manner, 26-[2-(1-imidazolyl)ethyl)]sulphinylpristinamycin $II_B$ (isomer $A_2$) (0.6 g) is obtained in the form of a yellow solid melting at about 170° C.

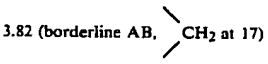
NMR spectrum (400 MHz, $CDCl_3$)

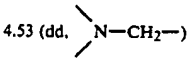
1.80 (s, $-CH_3$ at 33)
2.72 (mt, $-H_4$)



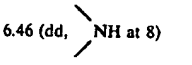



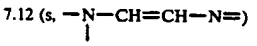



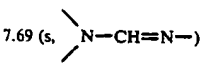




4.77 (d, $-H_{27}$)
5.52 (d, $-H_{13}$)
6.16 (d, $-H_{11}$)




8.16 (s, $-H_{20}$)

26-[2-(1-imidazolyl)ethyl]thiopristinamycin $II_B$ can be prepared by using a method similar to that described in Example 3, but starting from pristinamycin $II_A$ (14.35 g) and 2-(1-imidazolyl)ethanethiol (3.5 g), after stirring at 20° C. for 18 hours followed by purification by "flash" chromatography [eluent: ethyl acetate-methanol (80-20 by volume)] and concentrating fractions 34 to 59 to dryness under reduced pressure (2.7 kPa) at 30° C.; a yellow solid is obtained, which is stirred in ethyl ether (60 cc) and then separated off by filtration, to give 26-[2-(1-imidazolyl)ethyl]thiopristinamycin $II_B$ (isomers: 85% A, 15% B) (10.9 g) in the form of a yellow solid melting at about 160° C.

NMR spectrum: 1.53 (s, $-CH_3$ at 33 of B), 1.73 (s, $-CH_3$ at 33 of A), 2.74 (mt, $-H_4$ of A), 2.86 and 3.14 (2 dd, $>CH_2$ at 15 of A), 2.85 to 3.05 (mt, $-SCH_2-$), 3.11 (mt, $-H_{26}$ of A), 3.32 (mt, $-H_{26}$ of B), 3.82 (borderline AB, $>CH_2$ at 17 of A), 4.15 to 4.30 (mt, $-CH_2N>$), 4.58 (d, $-H_{27}$ of B), 4.68 (fine d, $-H_{27}$ of A), 5.44 (d, $-H_{13}$ of A), 6.16 (d, $-H_{11}$ of A), 6.83 (dd, >NH at 8 of A), 6.97 and 7.08 (2s, >N—CH=CHN< of B), 7.01 and 7.10 (2s, >N—CH=CHN< of A), 7.54 (s, >N—CH=N— of B), 7.61 (s, >N—CH=N— of A), 7.64 (mt, >NH at 8 of B), 7.82 (s, $-H_{20}$ of B), 8.09 (s, $-H_{20}$ of A).

2-(1-Imidazolyl)ethanethiol can be prepared by a method similar to that described in Example 11 for the preparation of the starting material, but starting from 2-(1-imidazolyl)ethanethiolacetate (21 g) and sodium methoxide (0.5 g). After purification by distillation, 2-(1-imidazolyl)ethanethiol (2.3 g) is obtained in the form of an oil [b.p. (20 Pa)=99.5° C.].

2-(1-Imidazolyl)ethanethiolacetate can be prepared by a method similar to that described in Example 11 for the preparation of the starting material, but starting from 2-(1-imidazolyl)ethanol (15 g), triphenylphosphine (70.2 g), diisopropyl azodicarboxylate (55.8 cc) and thiolacetic acid (21 cc). After purification by "flash" chromatography [eluent: methylene chloride (1500 c), followed by ethyl acetate-methanol (80-20 by volume)], 100-cc fractions being collected, and concentrating fractions 21 to 35 to dryness under reduced pressure (2.7 kPa) at 30° C., 2-(1-imidazolyl)ethylthioacetate (21.14 g) is obtained in the form of an orange-yellow oil which is used without further purification.

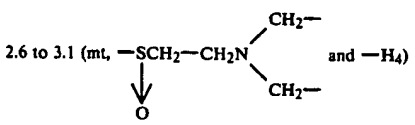
2-(1-Imidazolyl)ethanol can be prepared by a method similar to that described by J. Geibel et al., J. Am. Chem. Soc., 100, 3575 (1978).

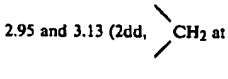
## EXAMPLE 15

By using a method similar to that described in Example 2, but starting from 26-(2-morpholinoethyl)thiopristinamycin $II_B$ (isomer A) (5.5 g), sodium bicarbonate (1.3 g), and 98% meta-chloroperbenzoic acid (1.4 g), after extraction of the reaction mixture, drying of the organic phase over magnesium sulphate, filtering and concentrating to dryness under reduced pressure (2.7 kPa) at 30° C., a light-yellow solid is obtained, which is stirred in isopropyl ether (100 cc), separated off by filtration, and then dried under reduced pressure (90 Pa) at 35° C. In this manner, 26-(2-morpholinoethyl)sulphinylpristinamycin $II_B$ (isomer $A_2$) (4.8 g) is obtained in the form of a light-yellow solid melting at about 126° C.

NMR spectrum:

1.77 (s, $-CH_3$ at 33)



-continued

3.20 (mt, $-H_{26}$)
3.78 (mt, $-CH_2-O-CH_2-$)

3.81 (s, $CH_2$ at 17)

4.85 (mt, $-H_{27}$)
5.53 (d, $-H_{13}$)
6.20 (d, $-H_{11}$)

6.53 (mf, NH at 8)

8.14 (s, $-H_{20}$)

26-(2-Morpholinoethyl)thiopristinamycin $II_B$ (isomer A) can be obtained by a method similar to that described in Example 1, but starting from pristinamycin $II_A$ (15 g) and 2-morpholinoethanethiol (6.3 g). After purification by "flash" chromatography [eluent: ethyl acetate-methanol (75-25 by volume)], 30-cc fractions being collected, and concentrating fractions 35 to 49 to dryness under reduced pressure (2.7 kPa) at 30° C., a beige solid (11 g) is obtained which is crystallized from acetonitrile (120 cc). In this manner, 26-(2-morpholinoethyl)thiopristinamycin $II_B$ (isomer A) (5.7 g) is obtained in the form of white crystals melting at 132° C.

NMR spectrum:

1.73 (s, $-CH_3$ at 33)

2.50 (mf, $-N(CH_2-)(CH_2-)$)

2.6 to 2.9 (mt, $-H_4$)

2.64 (mt, $N-CH_2-$)

2.79 (mt, $-SCH_2-$)

2.91 and 3.11 (2dd, $CH_2$ at 15)

3.37 (broad d, $-H_{26}$)

3.74 (mf, $O(CH_2-)(CH_2-)$)

3.83 (s, $CH_2$ at 17)

4.74 (broad s, $-H_{27}$)
5.45 (d, $-H_{13}$)
6.13 (d, $-H_{11}$)

-continued

6.28 (mf, NH at 8)

8.13 (S, $-H_{20}$)

2-Morpholinoethanethiol can be prepared by a method similar to that described by D. D. Reynolds et al., J. Org. Chem., 26, 5125 (1961).

## EXAMPLE 16

By using a method similar to that described in Example 1, but starting from 26-(2-butylaminoethyl)thiopristinamycin $II_B$ (80% isomer A, 20% isomer B) (5.8 g), trifluoroacetic acid (0.68 cc) and meta-chloroperbenzoic acid (1.8 g), and after purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)], 15-cc fractions being collected, and concentrating fractions 9 to 15 dryness under reduced pressure (2.7 kPa) at 30° C., 26-(2-butylaminoethyl)sulphinylpristinamycin $II_B$ (70% isomer $A_2$, 15% isomer $B_1$, 15% isomer $B_2$) (1.7 g) is obtained in the form of a yellow powder melting at about 140° C.

NMR spectrum (isomer $A_2$):

0.85 to 1.00 (mt, $-CH_3$ at 31 and 30 + chain $-CH_3$)

1.34 (mt, $-C\underline{H}_2CH_3$)

1.48 (mt, $-CH_2C\underline{H}_2CH_2CH_3$)

1.75 (s, $-CH_3$ at 33)

2.50 to 3.30 (mt, $-H_{26}$, $CH_2$ at 2, $-S(=O)-CH_2-CH_2-N(-CH_2-)-CH_2-$, $-H_4$)

3.80 (s, $CH_2$ at 17)

4.80 (d, $-H_{27}$)

5.50 (d, $-H_{13}$)

6.17 (d, $-H_{11}$)

6.40 (dd, NH at 8)

8.12 (s, $-H_{20}$)

After concentrating fractions 18 to 24 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-(2-butylaminoethyl)sulphinylpristinamycin $II_B$ (85% isomer $A_1$, 15% isomer $B_1$) (0.5 g) is obtained in the form of a yellow powder melting at about 170° C.

NMR spectrum (isomer $A_1$):

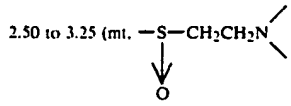
0.85 to 1.00 (mt, $-CH_3$ at 31, 30 and chain $-CH_3$)

1.33 (mt, $-C\underline{H}_2CH_3$)

-continued

1.47 (mt, $-CH_2\underline{CH_2}CH_2CH_3$)

1.71 (s, $-CH_3$ at 33)

2.50 to 3.25 (mt,  and $-H_4$)

3.79 (borderline AB,  at 17)

5.26 (d, $-H_{27}$)

5.44 (d, $-H_{13}$)

6.13 (d, $-H_{11}$)

6.62 (mt,  at 8)

8.10 (s, $-H_{20}$)

26-(2-Butylaminoethyl)thiopristinamycin $II_B$ (80% isomer A, 20% isomer B) can be prepared as described below in Example 17.

## EXAMPLE 17

By using a method similar to that described in Example 1, but starting from 26-(2-butylaminoethyl)thiopristinamycin $II_B$ (isomer B) (3.15 g), trifluoroacetic acid (0.37 cc) and meta-chloroperbenzoic acid (0.97 g), and after purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)], 15-cc fractions being collected, and concentrating fractions 18 to 35 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-(2-butylaminoethyl)sulphinylpristinamycin $II_B$ (65% isomer $B_1$, 35% isomer $B_2$) (1.18 g) is obtained in the form of a yellow powder melting at about 140° C.

NMR spectrum:

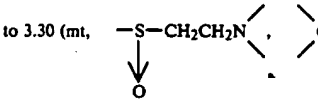
0.90 to 1.05 (mt, $-CH_3$ at 30 and 31 and chain $-CH_3$ of $B_1$ and $B_2$)

1.40 (mt, $-C\underline{H_2}CH_3$ of $B_1$ and $B_2$)

1.50 (mt, $-CH_2\underline{CH_2}CH_2CH_3$ of $B_1$ and $B_2$)

1.57 (s, $-CH_3$ at 33 of $B_1$ and $B_2$)

2.63 (t,  of $B_1$ and $B_2$)

2.65 to 3.30 (mt,  at 15, $-H_4$ of $B_1$ and $B_2$)

3.74 and 3.92 (2d,  at 17 of $B_1$)

3.73 and 3.94 (2d,  at 17 of $B_2$)

4.78 (d, $-H_{27}$ of $B_2$)

4.75 to 4.90 (mt, $-H_{13}$ and $-H_{14}$ of $B_1$ and $B_2$)

5.27 (d, $-H_{27}$ of $B_1$)

5.70 (2d, $-H_{11}$ of $B_1$ and $B_2$)

7.69 (dd,  at 8 of $B_2$)

7.79 (dd,  at 8 of $B_1$)

7.84 (s, $-H_{20}$ of $B_2$)

7.85 (s, $-H_{20}$ of $B_1$)

By using a method similar to that described in Example 3, but starting from pristinamycin $II_A$ (25 g) and 2-butylaminoethanethiol (6.34 g), and after purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)], 60-cc fractions being collected, and concentrating fractions 12 to 15 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-(2-butylaminoethyl)thiopristinamycin $II_B$ (isomer B) (3.15 g) is obtained in the form of a yellow powder melting at about 110° C. After concentrating fractions 15 to 25 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-(2-butylaminoethyl)thiopristinamycin $II_B$ (80% isomer A, 20% isomer B) (5.89 g) is obtained.

## EXAMPLE 18

By using a method similar to that described in Example 1, but starting from 26-(2-decylaminoethyl)thiopristinamycin $II_B$ (8.6 g), trifluoroacetic acid (0.9 cc) and meta-chloroperbenzoic acid (2.35 g) and after purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)], 40-cc fractions being collected, and concentrating fractions 12 to 15 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-(2-decylaminoethyl)sulphinylpristinamycin $II_B$ (80% isomer $A_2$) (1.5 g) is obtained in the form of a yellow powder melting at about 128° C.

NMR spectrum: 0.88 (t, $-(CH_2)_9-CH_3$), 1.30 ([m, $(>CH_2)_8$], 1.50 [m$(>CH_2)_8$], 1.77 (s, $-CH_3$ at 33), 4.81 (d, $-H_{27}$), 5.51 (d, $-H_{13}$), 6.19 (d, $-H_{11}$), 6.53 (mt, >NH at 8), 8.13 (s, $-H_{20}$).

After concentrating fractions 15 to 19 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-(2-decylaminoethyl)sulphinylpristinamycin $II_B$ (mixture of isomers) (2.51 g) is obtained in the form of a yellow powder melting at about 124° C.

NMR spectrum (mixture of isomers: 50% type $A_2$, 15% $A_1$, 20% $B_1$ and 15% $B_2$), 1.54 (s, $-CH_3$ at 33 of $B_1$ and $B_2$), 3.72 and 3.88 (2 d, $>CH_2$ at 17 of $B_1$), 3.70 and 3.92 (2d, $>CH_2$ at 17 of $B_2$), 4.75 (d, $-H_{27}$ of $B_2$), 5.25 (d, $-H_{27}$ of $B_1$), 7.67 (dd, >NH at 8 of $B_2$), 7.77 (dd, >NH at 8 of $B_1$), 7.81 (s, $-H_{20}$ of $B_1$ and $B_2$),

(characteristic peaks of isomers $A_2$ and $A_1$, identical to those mentioned above and below, respectively).

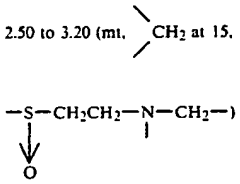
An aqueous solution containing 1% of 26-(2-decylaminoethyl)sulphinylpristinamycin $II_B$ in the form of hydrochloride is obtained with:

| | |
|---|---|
| 26-(2-decylaminoethyl)sulphinylpristinamycin $II_B$ | 15 mg |
| 0.1 N hydrochloric acid | 0.2 cc |
| distilled water q.s. | 1.5 cc. |

After concentrating fractions 20 to 24 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-(2-decylaminoethyl)sulphinylpristinamycin $II_B$ (isomers: 60% $A_1$, 20% $A_2$, 20% $B_1$) (1.12 g) is obtained in the form of a yellow powder melting at about 136° C.

NMR spectrum (isomer $A_1$):

2.50 to 3.20 (mt, $CH_2$ at 15, $-H_4$ and



3.82 (borderline AB, $CH_2$ at 17)

5.27 (d, $-H_{27}$)
5.46 (d, $-H_{13}$)
6.15 (d, $-H_{11}$)

6.62 (mt, NH at 8)

8.12 (s, $-H_{20}$)

26-(2-Decylaminoethyl)thiopristinamycin $II_B$ can be prepared as follows:

By using a method similar to that described in Example 3, but starting from pristinamycin $II_A$ (5.25 g) and 2-decylaminoethanethiol (3.26 g), and after purification by "flash" chromatography [eluent: methylene chloride-methanol (95-5 by volume)], and concentrating fractions 20 to 43 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-(2-decylaminoethyl)thiopristinamycin $II_B$ (1.2 g) is obtained in the form of a yellow powder melting at about 80° C.

NMR spectrum (70-30 mixture of A and B isomers):

0.88 (t, $-CH_3$)

1.30
1.53 } (mt, $-(CH_2)_8-$)

1.54 (s, $-CH_3$ at 33 of B)
1.72 (s, $-CH_3$ at 33 of A)

2.6 to 3 (mt, $-SCH_2-CH_2-N-CH_2-$)

3.38 (broad d, $-H_{26}$ of A)
3.50 (mt, $-H_{26}$ of B)
4.64 (d, J = 3.5, $-H_{27}$ of B)
4.72 (broad s, $-H_{27}$ of A)

-continued

7.80 (s, $-H_{20}$ of B)
8.12 (s, $-H_{20}$ of A)

## EXAMPLE 19

By using a method similar to that described in Example 1, starting from 26-(2-cyclohexylaminoethyl)sulphinylpristinamycin $II_B$ (isomers: 80% A, 20% B) (4.4 g), trifluoroacetic acid (0.5 cc) and meta-chloroperbenzoic acid (1.15 g), and after purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)], 40-cc fractions being collected, and concentrating fractions 24 to 29 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-(2-cyclohexylaminoethyl)sulphinylpristinamycin $II_B$ (90% isomer $A_2$) (0.38 g) is obtained in the form of a light-yellow powder melting at about 166° C.

NMR spectrum:

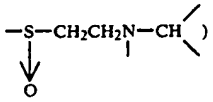
1.05 to 1.35 [mt, cyclohexyl $CH_2$ (partly)]

1.77 (s, $-CH_3$ at 33)

1.55 to 2.25 [mt, $CH_2$ at 25, $-H_{29}$ and

cyclohexyl $CH_2$ (partly)]

2.45 to 3.35 (mt, $-H_{26}$, $CH_2$ at 15, $-H_4$ and



3.82 (s, $CH_2$ at 17)

4.82 (d, $-H_{27}$)
5.52 (d, $-H_{13}$)
6.19 (d, $-H_{11}$)

6.38 (dd, NH at 8)

8.14 (s, $-H_{20}$)

26-(2-Cyclohexylaminoethyl)thiopristinamycin $II_B$ can be obtained as follows:

By using a method similar to that described in Example 3, but starting from pristinamycin $II_A$ (5.25 g) and 2-cyclohexylaminoethanethiol (3.6 g), and after purification by "flash" chromatography [eluent: chloroform-methanol (93-7 by volume)] and concentrating fractions 7 to 18 to dryness under reduced pressure (2.7 kPa) at

30° C., 26-(2-cyclohexylaminoethyl)thiopristinamycin $II_B$ (1.7 g) is obtained in the form of a beige powder melting at about 120° C.

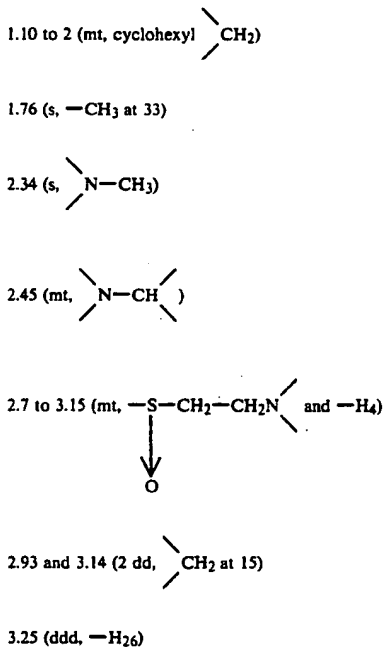
NMR spectrum: 1 to 1.4 [mt, cyclohexyl $>CH_2$ (partly)], 1.54 (s, $-CH_3$ at 33 isomer B), 1.73 (s, $-CH_3$ at 33 isomer A), 1.6 to 2 [mt, cyclohexyl $>CH_2$ (partly)], 2.80 (mt, $>NCH_2-$), 2.93 (t, $-SCH_2-$), 3.36 (broad d, $-H_{26}$ isomer A), 3.50 (mt, $-H_{26}$ isomer B), 4.64 (d, J=3, $-H_{27}$ isomer B), 4.72 (broad s, $-H_{27}$ isomer A), 6.50 (mt, $-NH_8$ isomer A), 7.75 (mt, $-NH_8$ isomer B), 7.80 (s, $-H_{20}$ isomer B), 8.12 (s, $-H_{20}$ isomer A).

2-Cyclohexylaminoethanethiol can be prepared according to the method described by D. D. Reynolds, M. K. Massad, D. L. Fields and D. L. Johnson, J. Org. Chem. 26, 5109 (1961).

## EXAMPLE 20

By using a method similar to that described in Example 2, but starting from 26-(N-cyclohexyl-N-methyl-2-aminoethyl)thiopristinamycin $II_B$ (isomers: 80% A, 20% B) (5 g), sodium bicarbonate (1.17 g) and 98% metachloroperbenzoic acid (1.2 g), after purification by "flash" chromatography [eluent: dichloromethane-methanol (80-20 by volume)], 30-cc fractions being collected, and concentrating fractions 40 to 60 to dryness under reduced pressure (2.7 kPa) at 30° C., a yellow solid (3.5 g) is obtained, which is purified again by "flash" chromatography [eluent: ethyl acetate-methanol (80-20 by volume)], 25-cc fractions being collected. After concentrating fractions 11 to 18 to dryness under reduced pressure (2.7 kPa) at 30° C., a yellow solid (1.2 g) is obtained, which is stirred in ethyl ether (30 cc), separated off by filtration and then dried under reduced pressure (90 Pa) at 35° C. In this manner, 26-(N-cyclohexyl-N-methyl-2-aminoethyl)sulphinyl-pristinamycin $II_B$ (isomer $A_2$) (1.1 g) is obtained in the form of a yellow powder melting at about 126° C.

NMR spectrum:

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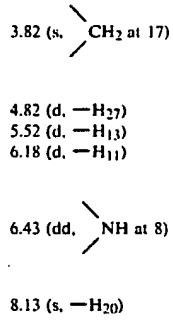



26-)N-Cyclohexyl-N-methyl-2-aminoethyl)thiopristinamycin $II_B$ (isomers: 80% A, 20% B) can be obtained by a method similar to that described in Example 3 for the preparation of the starting material, but starting from pristinamycin $II_A$ (10.5 g) and N-cyclohexyl-N-methyl-2-aminoethanethiol (4 g). After purification by "flash" chromatography [eluent: ethyl acetate-methanol (80-20 by volume)], 30-cc fractions being collected, and concentrating fractions 42 to 96 to dryness under reduced pressure (2.7 kPa) at 30° C., a yellow solid is obtained which is stirred in isopropyl ether (80 cc), separated off by filtration and then dried under reduced pressure (90 Pa) at 35° C. In this manner, 26-(N-cyclohexyl-N-methyl-2-aminoethyl)thiopristinamycin $II_B$ (isomers: 80% A and 20% B) (7.9 g) is obtained in the form of a yellow powder melting at about 116° C.

NMR spectrum (80/20 mixture of two isomers A and B): 1.25 and 1.6 to 1.9 (mt, cyclohexyl $>CH_2$ for A and B), 1.56 (s, $-CH_3$ at 33 of B), 1.73 (s, $-CH_3$ at 33 of A), 2.25 to 2.5 (mt, cyclohexyl $>CH-$ for A and B), 2.32 (s, $>N-CH_3$ of B), 2.35 (s, $>N-CH_3$ of A), 2.6 to 2.8 (mt, $-H_4$ of A and B), 2.78 (borderline AB, $-SCH_2CH_2N<$ of A and B), 2.9 and 3.14 (2dd, $>CH_2$ at 15 of A), 3.41 (broad d, $-H_{26}$ of A), 3.73 and 3.91 (2d, $>CH_2$ at 17 of B), 3.83 (s, $>CH_2$ at 17 of A), 4.65 (d, $-H_{27}$ of B), 4.76 (broad s, $-H_{27}$ of A), 5.49 (d, $-H_{13}$ of A), 6.16 (d, $-H_{11}$ of A), 6.36 (mf, $>NH$ at 8 of A), 7.73 (mf, $>NH$ at 8 of B), 7.82 (s, $-H_{20}$ of B), 8.13 (s, $-H_{20}$ of A).

N-Cyclohexyl-N-methyl-2-aminoethanethiol can be obtained as follows:

A 6N aqueous solution of sodium hydroxide (23 cc) is added under a nitrogen atmosphere to S-(N-cyclohexyl-N-methyl-2-aminoethyl)isothiouronium dihydrochloride (20 g). After being stirred at 100° C. for 2 hours, the mixture is cooled to 25° C. and then a concentrated solution of hydrochloric acid is added to it to a pH of 9. The solution is washed with dichloromethane (3×50 cc) and then the organic phases are combined, dried over magnesium sulphate, filtered, and then concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. to give an oil, which is purified by distillation under reduced pressure (130 Pa). N-Cyclohexyl-N-methyl-2-aminoethanethiol (4.3 g) is obtained in the form of a colourless liquid [b.p. (130 Pa) =68° C.].

N-Cyclohexyl-N-methyl-2-aminoethanethiouronium dihydrochloride can be obtained as follows:

Thiourea (10.7 g) is added to 2-(N-cyclohexyl-N-methyl-amino)-1-chloroethane hydrochloride (30 g) in ethanol (300 cc). The solution obtained is heated for 18 hours at 78° C. After cooling, the white solid obtained is filtered off and then washed with ethanol. In this

manner, N-cyclohexyl-N-methyl-2-aminoethanethiouronium dihydrochloride (21.5 g) is obtained in the form of a white solid melting at 248° C.

2-(N-Cyclohexyl-N-methyl-amino)-1-chloroethane hydrochloride can be obtained as follows:

N-Cyclohexyl-N-methyl-2-aminoethanol (25 g) is added dropwise to thionyl chloride (120 cc) and then the mixture is heated for 24 hours at 70° C. After the excess thionyl chloride has been distilled off, the orange oil obtained is stirred into ethyl ether (200 cc) to give a white solid, which is separated off by filtrattion and then washed with ether. 2-(N-Cyclohexyl-N-methyl-amino)-1-chloroethane (30 g) is obtained in the form of a white solid melting at 154° C.

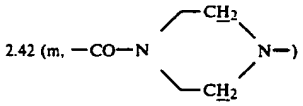
## EXAMPLE 21

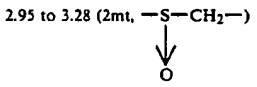
By using a method similar to that described in Example 1, but starting from 26-[(4-methyl-1-piperazinyl)-2-carbonyloxyethyl]thiopristinamycin $II_B$ (isomer A) (4.3 g) trifluoroacetic acid (0.45 cc) and meta-chloroperbenzoic acid (1.2 g), and after purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)], 30-cc fractions being collected, and concentrating fractions 42 to 56 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-[(4-methyl-1-piperazinyl)-2-carbonyloxyethyl]sulphinylpristinamycin $II_B$ (isomer $A_2$) (1.2 g) is obtained in the form of a light-yellow powder melting at about 135° C.

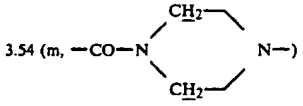
NMR spectrum:

1.78 (s, $-CH_3$ at 33)

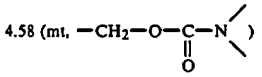
2.32 (s,  )

2.42 (m,  )

2.95 to 3.28 (2mt,  )

3.54 (m,  )

3.82 (s,  )

4.58 (mt,  )

4.82 (d, $-H_{27}$)
5.50 (d, $-H_{13}$)
6.20 (d, $-H_{11}$)

6.39 (dd,  )

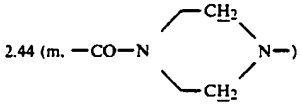
8.14 (s, $-H_{20}$)

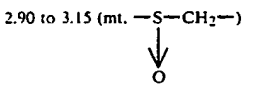
After concentrating fractions 65 to 95 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-[(4-methyl-1-piperazinyl)-2-carbonyloxyethyl]sulphinylpristinamycin $II_B$ (isomer $A_1$) (0.65 g) is obtained in the form of a light-yellow powder melting at about 140° C.

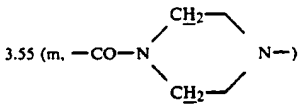
NMR spectrum:

1.75 (s, $-CH_3$ at 33)

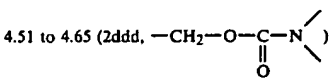
2.34 (s,  )

2.44 (m,  )

2.90 to 3.15 (mt,  )

3.55 (m,  )

3.83 (s,  )

4.51 to 4.65 (2ddd,  )

5.28 (d, $-H_{27}$)
6.19 (d, $-H_{11}$)

6.55 (dd,  )

8.14 (s, $-H_{20}$)

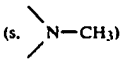
26-[(4-Methyl-1-piperazinyl)-2-carbonyloxyethyl]thiopristinamycin $II_B$ can be prepared as follows:

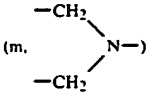
By using a method similar to that described in Example 3, starting from pristinamycin $II_A$ (5.25 g) and (4-methyl-1-piperazinyl)-2-carbonyloxyethanethiol (3.76 g), and after purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)] and concentrating fractions 10 to 18 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-[(4-methyl-1-piperazinyl)-2-carbonyloxyethyl]thiopristinamycin $II_B$ is obtained in the form of a beige powder melting at about 100° C.

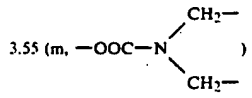
NMR spectrum:

1.54 (s, $-CH_3$ at 33 of isomer B)
1.73 (s, $-CH_3$ at 33 of isomer A)

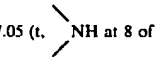
-continued

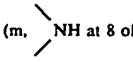
2.3 (s,  )

2.4 (m,  )

3.55 (m,  )

3.98 (mt, $-CH_2-OCO-$)
4.59 (d, J = 4, $-H_{27}$ of isomer B)
4.69 (broad s, $-H_{27}$ of isomer A)

7.05 (t,  )

7.7 (m,  )

7.80 (s, $-H_{20}$ of isomer B)
8.10 (s, $-H_{20}$ of isomer A)

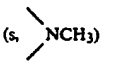
(4-Methyl-1-piperazinyl)-2-carbonyloxyethanethiol can be prepared according to the method described by D. D. Reynolds, D. L. Fields and D. L. Johnson, J. Org. Chem. 26, 5111 (1961).

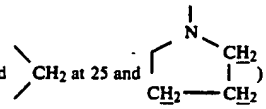
## EXAMPLE 22

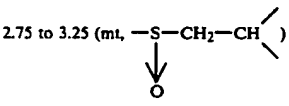
By using a method similar to that described in Example 1, but starting from 26-[(S)-1-methyl-2-pyrrolidinyl]methylthiopristinamycin $II_B$ (isomer A) (7.8 g), trifluoroacetic acid (0.91 cc) and meta-chloroperbenzoic acid (2.4 g), and after purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)], 60-cc fractions being collected, and concentrating fractions 26 to 36 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-[(S)-1-methyl-2-pyrrolidinyl]methylsulphinylpristinamycin $II_B$ (isomer $A_2$) (2.3 g) is obtained in the form of a light-yellow powder melting at about 140° C.

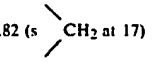
NMR spectrum:

1.76 (s, $-CH_3$ at 33)

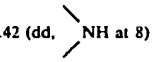
2.48 (s,  )

1.70 to 2.60 (mt, $-H_{29}$ and  )

2.75 to 3.25 (mt,  )

3.82 (s  )

4.81 (d, $-H_{27}$)
5.52 (d, $-H_{13}$)
6.20 (d, $-H_{11}$)

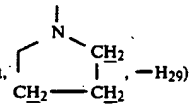
6.42 (dd,  )

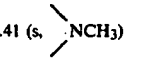
8.14 (s, $-H_{20}$)

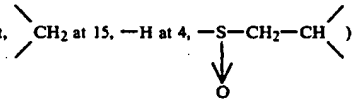
After concentrating fractions 46 to 59 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-[(S)-1-methyl-2-pyrrolidinyl]methylsulphinylpristinamycin $II_B$ (isomer $A_1$) (1.1 g) is obtained in the form of a light-yellow powder melting at about 148° C.

NMR spectrum:

1.73 (s, $-CH_3$ at 33)

1.70 to 2.50 (mt,  )

2.41 (s,  )

2.65 to 3.25 (mt,  )

3.82 (borderline AB,  )

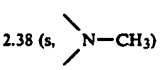
5.45 (d, $-H_{13}$)
6.17 (d, $-H_{11}$)
8.11 (s, $-H_{20}$)

26-(1-Methyl-2-pyrrolidinyl)methylthiopristinamycin $II_B$ can be prepared as follows:

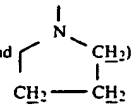
By using a method similar to that described in Example 3, but starting from pristinamycin $II_A$ (10.5 g) and [(S)-1-methyl-2-pyrrolidinyl]methanethiol (3.14 g), and after purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)] and concentrating fractions 20 to 35 to dryness under reduced pressure (2.7 kPa) at 30° C., the A isomer (7.8 g) is obtained in the form of a yellow powder melting at approximately 120° C.

NMR spectrum:

1.70 (s, $-CH_3$ at 33)

2.38 (s,  )

-continued

1.70 to 2.50 (mt, $-H_{29}$, $CH_2$ at 25 and $CH_2$) 

2.6 to 3.20 (mt, $-S-CH_2-CH$) 

3.82 (s, $CH_2$ at 17) 

4.73 (d, $-H_{27}$)
5.45 (d, $-H_{13}$)
6.15 (d, $-H_{11}$)

6.41 (dd, NH at 8) 

8.11 (s, $-H_{20}$)

A 4N aqueous solution of sodium hydroxide (100 cc) is added to crude S-[(S)-1-methyl-2-pyrrolidinylmethyl-]isothiouronium dihydrochloride (25 g) dissolved in distilled water (100 cc), and then the mixture is stirred for 2 hours at 90° C. under a nitrogen atmosphere. The reaction mixture is cooled to 0° C., a 12N aqueous solution of hydrochloric acid (25 cc) is added to it, and then it is extracted with methylene chloride (2×200 cc). The organic phase is dried over sodium sulphate, filtered, and then concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. In this manner [(S)-1-methyl-2-pyrrolidinyl]methanethiol (5.9 g) is obtained in the form of a light-yellow oil, which is used in the subsequent reaction without additional purification.

$R_f$=0.15; silica gel chromatographic plate; eluent: chloroform-methanol (90-10 by volume).

Thiourea (10.7 g) is added to [(S)-1-methyl-2-pyrrolidinyl]chloromethane hydrochloride (11.9 g) dissolved in ethanol (50 cc), and then the mixture is stirred for 48 hours under reflux. The mixture is concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. The residue is taken up again with hot ethanol (100 cc) and then filtered through activated plant charcoal. After the filtrate has been concentrated to dryness under reduced pressure (2.7 kPa) at 40° C., a light-yellow oil (25 g) consisting of S-[(S)-1-methyl-2-pyrrolidinylmethyl]isothiouronium dihydrochloride and excess thiourea, is obtained.

Rf=0.1; silica gel chromatographic plate; eluent: chloroform-methanol (90-10 by volume).

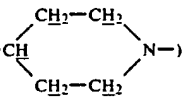
[(S)-1-Methyl-2-pyrrolidinyl]chloromethane hydrochloride can be prepared according to the method described by T. Hayashi et al., J. Org. Chem., 48, 2195 (1983).

## EXAMPLE 23

By using a method similar to that described in Example 1, but starting from 26-(1-methyl-4-piperidinyl)-thiopristinamycin $II_B$ (2.6 g), trifluoroacetic acid (0.3 cc) and meta-chloroperbenzoic acid (0.8 g), and after purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)], 40-cc fractions being collected, and concentrating fractions 20 to 35 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-(1-methyl-4-piperidinyl)sulphinylpristinamycin $II_B$ (isomer $A_2$) (0.33 g) is obtained in the form of a yellow powder melting at about 170° C.

NMR spectrum:

1.76 (s, $-CH_3$ at 33)

2.2 to 3.00 (mt, $-CH$  $N-$)

2.32 (s, $N-CH_3$) 

3.82 (s, $CH_2$ at 17) 

4.85 (d, $-H_{27}$)
5.50 (d, $-H_{13}$)
6.19 (d, $-H_{11}$)

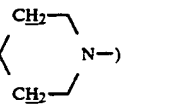
6.37 (dd, NH at 8) 

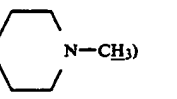
8.15 (s, $-H_{20}$)

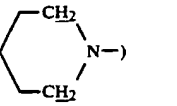
26-(1-Methyl-4-piperidinyl)thiopristinamycin $II_B$ can be obtained as follows:

By using a method similar to that described in Example 3, but starting from pristinamycin $II_A$ (3.15 g) and 2-methyl-4-piperidinethiol (1.6 g), and adding triethylamine (0.6 g) to the reaction mixture, and after purification by "flash" chromatography [eluent: methylene chloride-methanol (92-8 by volume)], and concentrating fractions 4 to 20 to dryness under reduced pressure (2.7 kPa) at 30° C., 26-(1-methyl-4-piperidinyl)thiopristinamycin $II_B$ (0.9 g) is obtained in the form of a yellow powder melting at about 180° C.

NMR spectrum:

2.10 (m, 4H: $-S-$  $N-$)

2.25 (s, 3H: $-S-$  $N-CH_3$)

2.80 (m, 4H: $-S-$  $N-$)

3.55 (m, 1H: $-H_{26}$)
4.62 (m, 1H: $-H_{27}$)
7.70 (m, 1H: $-H_8$)
8.10 (s, 1H: $-H_{20}$)

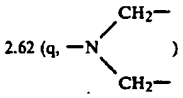
2-Methyl-4-piperidinethiol can be prepared by the method described by H. Barrer and R. E. Lyle, J. Org. Chem., 27, 641 (1962).

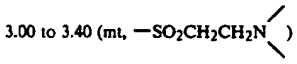
## EXAMPLE 24

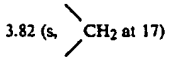
Trifluoroacetic acid (0.92 cc) is added under a nitrogen atmosphere to 26-(2-diethylaminoethyl)thiopristinamycin $II_B$ (7.8 g) dissolved in methanol (60 cc), at 0° C. After 15 minutes at 0° C., the temperature is raised to 15° C., and then selenium dioxide (1.37 g) is added. When all the selenium dioxide has dissolved, a 30% strength aqueous solution of hydrogen peroxide (7 cc) is added slowly at a temperature below 25° C. After being stirred at 25° C. for 1 hour, the reaction mixture is cooled to 10° C., a saturated aqueous solution of sodium bicarbonate (50 cc) is added to it, and then it is extracted with methylene chloride (4×50 cc). The organic phases are combined, dried over magnesium sulphate, filtered, and then concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. The yellow solid obtained is purified by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)], 40-cc fractions being collected. After concentrating fractions 31 to 38 to dryness under reduced pressure (2.7 kPa) at 30° C., a yellow solid is obtained, which is purified by "flash" chromatography [eluent: ethyl acetate-methanol (80-20 by volume)], 40-cc fractions being collected. After concentrating fractions 27 to 33 to dryness under reduced pressure, a white solid is obtained, which is stirred in ethyl ether (50 cc), separated off by filtration and then dried under reduced pressure (90 Pa) at 30° C. In this manner, 26-(2-diethylaminoethyl)sulphonylpristinamycin $II_B$ (isomer A) (0.5 g) is obtained in the form of a white solid melting at about 150° C.

NMR spectrum:

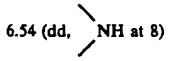
0.97 (d, $-CH_3$ at 30 and 31 and ethyl $-CH_3$)
1.75 (s, $-CH_3$ at 33)




5.34 (d, $-H_{13}$)
5.43 (d, $-H_{13}$)
6.16 (d, $-H_{11}$)



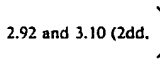

8.10 (s, $-H_{20}$)

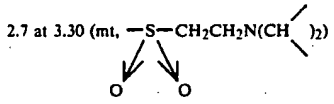
## EXAMPLE 25

A method similar to that described in Example 24 is used, but starting from 26-(2-diisopropylaminoethyl)thiopristinamycin $II_B$ (isomer A) (6.86 g), trifluoroacetic acid (0.77 cc), selenium dioxide (1.15 g), and a 30% strength aqueous solution of hydrogen peroxide (6.33 cc). After purification by "flash" chromatography [eluent: ethyl acetate-methanol (80-20 by volume)], 40-cc fractions being collected, and concentrating fractions 28 to 31 to dryness under reduced pressure (2.7 kPa) at 30° C., a yellow solid (0.7 g) is obtained, which is purified again by "flash" chromatography [eluent: ethyl acetate-methanol (85-15 by volume)], 30-cc fractions being collected. After concentrating fractions 26 to 33 to dryness under reduced pressure, a yellow solid is obtained, which is stirred in ethyl ether (30 cc), separated off by filtration and then dried under reduced pressure (90 Pa) at 30° C. 26-(2-Diisopropylaminoethyl)sulphonylpristinamycin $II_B$ (isomer A) (0.6 g) is obtained in the form of a light-yellow solid melting at about 140° C.

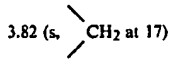
NMR spectrum:

1.06 (d, isopropyl $-CH_3$)
1.75 (s, $-CH_3$ at 33)
2.79 (mt, $-H_4$)

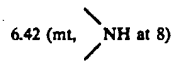



3.52 (broad d, $-H_{26}$)




5.27 (fine d, $-H_{27}$)
5.47 (d, $-H_{13}$)
6.17 (d, $-H_{11}$)




8.12 (s, $-H_{20}$)

## Reference Example 1

Pristinamycin $I_A$ (0.5 g) and sodium cyanoborohydride (20 mg) are added to a solution of 3-dimethylaminopropylamine (0.41 cc) in methanol (15 cc) containing a 2N methanolic solution (2.4 cc) of hydrogen chloride gas, maintained at 55° C. The solution obtained is then allowed to regain a temperature of about 20° C. over approximately 2 hours, and it is then concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. The residue obtained is triturated with a mixture of methylene chloride (50 cc) and of a saturated aqueous solution of sodium bicarbonate (50 cc); the organic phase is separated off and the aqueous phase is extracted twice with methylene chloride (20 cc in total). The organic phases are combined, dried over magnesium sulphate, filtered, and then concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. The residue obtained is purified by "flash" chromatography [eluent: chloroform-methanol (80-20 by volume)]. Fractions 15 to 30 are combined and concentrated to dryness

under reduced pressure (2.7 kPa) at 30° C.; the residue obtained is triturated with ethyl ether (5 cc), filtered off and dried under reduced pressure (0.027 kPa) at 20° C. In this manner 5γ-deoxy(3-dimethylaminopropyl)-5γ-aminopristinamycin $I_A$ (60 mg) is obtained in the form of a cream-colored powder melting at about 160° C.

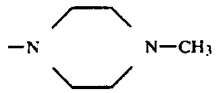
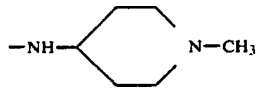
The complete NMR spectrum shows the following characteristics:

| δ (ppm) | Form of signal | Attribution |
|---|---|---|
| 8.40 | d | 6 NH |
| 8.25 | d | 1 NH |
| 7.55 | dd | $H_6$ |
| 7.05 | m | $6\gamma + 6\delta + 6\epsilon$ |
| 7 | dd | $H_4$ |
| 6.90 | dd | $H_5$ |
| 6.70 | d | $4\delta + 4\epsilon$ |
| 6.40 | d | |
| 6.50 | d | 2 NH |
| 5.75 | ddd | $1\beta$ |
| 5.45 | d | $6\alpha$ |
| 5.25 | dd | $4\alpha$ |
| 5 | s (broad) | $5\alpha$ |
| 4.75 | dd | $1\alpha$ |
| 4.60 | m | $2\alpha$ |
| 4.45 | (d broad) | $5\epsilon_1$ |
| 4.40 | dd | $3\alpha$ |
| 3.4 | (dd broad) | $3\delta_1$ |
| 3.20 | (dd broad) | $3\delta_2$ |
| 3 | s | 4 $CH_3$ |
| 3 | m | $5\gamma + 4\beta_1$ *and* 2 |
| 2.80 | s | 4 $N(CH_3)_2$ |
| 2.65 | t | $-NCH_2-$ (chain) |
| 2.35 | m | $5\epsilon_2 + 5\beta_1$ |
| 2.25 | t | $-NCH_2-$ (chain) |
| 2.20 | s | $-N(CH_3)_2$ (chain) |
| 1.60 | m | $-CH_2-$ (chain) $2\beta + 3\gamma$ |
| 1.25 | d | $1\gamma$ |
| 0.90 | t | $2\gamma$ |
| 0.50 | dddd | $5\beta_2$ |

An aqueous solution at a concentration of 10% of 5γ-deoxy-(3-dimethylaminopropyl)-5γ-amino-pristinamycin $I_A$ (product A), in the form of hydrochloride, is obtained with:

| | |
|---|---|
| product A | 0.1 g |
| 2 N hydrochloric acid | 0.52 cc |
| distilled water q.s. | 1 cc |

By using a method similar to that described in the reference Example 1, the following synergistins of general formula (V), which can be combined with the products according to the invention, are prepared:
[The symbols ═══, Z and $R_1$ are defined as at (1) for the general formula (V)].

| Reference example | Y | X | (1) Melting point (2) Solubility |
|---|---|---|---|
| 2 | $-N(CH_3)_2$ | $-NH(CH_2)_2N(CH_3)_2$ | (1) Yellow powder M. abt 180° C. (2) 10% aqueous solution of hydrochloride |
| 3 | $-N(CH_3)_2$ |  | (1) White powder M. abt. 195° C. (2) 10% aqueous solution of hydrochloride |
| 4 | $-N(CH_3)_2$ |  | (1) Beige powder (2) M. abt. 195° C. 3.7% aqueous solution of hydrochloride |
| 5 | $-N(CH_3)_2$ | $-NHOH$ | (1) White powder M. abt. 170° C. (2) 10% aqueous solution of hydrochloride |
| 6 | $-N(CH_3)_2$ | $-NH(CH_2)_3OH$ | (1) Cream powder M. abt. 160° C. (2) 2% aqueous solution of hydrochloride |
| 7 | $-H$ | $-NH(CH_2)_3N(CH_3)_2$ | (1) Beige powder M. abt. 140° C. (2) 10% aqueous solution of hydrochloride |

## Reference Example 8

A 5N ethanolic solution (2.8 cc) of dimethylamine, followed by a 5N methanolic solution (2 cc) of hydrogen chloride gas are added to a solution of pristinamycin $I_A$ (2 g) in methanol (25 cc). Sodium cyanoborohydride (76 mg) are added to the solution thus obtained, and the mixture is then stirred at a temperature of about 20° C. for 48 hours. The reaction mixture is then concentrated to dryness under reduced pressure (2.7 pKa) at 30° C. The residue is triturated with a mixture of methylene chloride (25 cc) and of a saturated aqueous solution of sodium bicarbonate (25 cc); the organic phase is separated off and the aqueous phase is extracted twice with methylene chloride (50 cc in total). The organic phases are combined, dried over magnesium sulphate, filtered, and then concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. The residue is purified by "flash" chromatography [eluent: chloroform-methanol (92-8 by volume)]. Fractions 5 to 12 are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. In this manner 5γ-deoxy-5γ-dimethylaminopristinamycin $I_A$ (0.7 g) is obtained in the form of a beige powder melting at about 170° C.

NMR spectrum: 0.70 (dt, 1H: $5\beta_2$), 2.10 to 2.60 (m, 4H: $5\delta_1+5\delta_2+5\beta_1+5\gamma$) 2.15 (s, 3H×0.8: $-N(CH_3)_2$ 1st isomer), 2.20 (s, 3H×0.2: $-N(CH_3)_2$ 2nd isomer).

An aqueous solution at a concentration of 2% of 5γ-deoxy-5γ-dimethylaminopristinamycin $I_A$ (product B), in the form of hydrochloride, is obtained with:

| | |
|---|---|
| product B | 0.05 g |
| 0.1 N hydrochloric acid | 0.56 cc |
| distilled water q.s. | 2.5 cc |

Reference Example 9

By using a method similar to that described in reference Example 8, 5γ-deoxy-5γ-methylaminopristinamycin $I_A$ (0.35 g) is obtained in the form of a yellow powder melting at about 185° C.

An aqueous solution at a concentration of 1% of 5γ-deoxy-5γ-methylaminopristinamycin $I_A$, in the form of hydrochloride, is obtained.

Reference Example 10

By using a method similar to that described in reference Example 8, 5γ-deoxy-5γ-[N-(2-dimethylaminoethyl)-N-methylamino]pristinamycin $I_A$ is obtained in the form of a white powder melting at about 120° C.

An aqueous solution at a concentration of 10% of 5γ-deoxy-5γ-[N-(2-dimethylaminoethyl)-N-methylamino]pristinamycin $I_A$ (product D), in the form of hydrochloride, is obtained.

Reference Example 11

A 3-Å molecular sieve (5 g) is added to a solution of pristinamycin $I_A$ (3 g), 4-diethylamino-2-methylbutylamine (3.3 g), sodium cyanoborohydride (0.11 g) and a 5N methanolic solution (9 cc) of hydrogen chloride gas in methanol (75 cc). The suspension obtained is stirred at a temperature of about 20° C. for 4 days, and is then filtered; the filtrate is concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. The residue is triturated with a mixture of methylene chloride (50 cc) and a saturated aqueous solution of sodium bicarbonate (50 cc); the organic phase is separated off and the aqueous phase is extracted twice with methylene chloride (50 cc in total). The organic phases are combined, dried over magnesium sulphate, filtered and then concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. The residue is purified by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)]. In this manner, 5γ-deoxy-15 5γ-(4-diethylamino-2-methylbutyl-)aminopristinamycin $I_A$ (0.7 g) is obtained in the form of a beige powder melting at about 160° C.

NMR spectrum:

1.10 (mt, 9H: $-N(CH_2\underline{CH_3})_2$ + $-\underset{|}{CH}-\underline{CH_3}$)

ca 1.7 (m, 4H: $-\underline{CH_2}-\underline{CH_2}-CH_2-N(C_2H_5)_2$)
2.90 (m, 6H: $-\underline{CH_2}N(\underline{CH_2}CH_3)_2$)
7.70 (mt, 1H × 0.45: 1'$H_6$ 1st isomer)
7.77 (mt, 1H × 0.55: 1'$H_6$ 2nd isomer)

An aqueous solution at a concentration of 10% of 5γ-deoxy-5γ-(4-diethylamino-2-methylbutyl)aminopristinamycin $I_A$ (product F) in the form of hydrochloride, is obtained with:

| | |
|---|---|
| product F | 0.1 g |
| 0.1 N hydrochloric acid q.s. | 1 cc |

Reference Example 12

Sodium cyanoborohydride (0.7 g) is added to a solution of 5γ-deoxy-5γ-hydroxyiminopristinamycin $I_A$ (12.5 g) in methanol (300 cc) containing a 2N methanolic solution (10 cc) of hydrogen chloride gas. The solution obtained is stirred at a temperature of about 20° C. for 2 days, and is then concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. The residue is triturated in a mixture of methylene chloride (200 cc) and a saturated aqueous solution of sodium bicarbonate (100 cc); the organic phase is separated off and the aqueous phase is extracted with methylene chloride (100 cc). The organic phases are combined, dried over magnesium sulphate, filtered, and concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. After purification by "flash" chromatography [eluent: chloroform-methanol (95-5 by volume)], 5γ-deoxy-5γ-hydroxyaminopristinamycin $I_A$ (6.8 g) is obtained in the form of a white powder melting at about 170° C.

NMR spectrum: 0.4 (m, 1H: $5\beta_2$), 2.45 (d, 1H: $5\beta_1$), 3.1 (d: 5γ in complex unresolved bands), 7.80 (mt, 1H×0.75: 1'$H_6$ 1st isomer), 7.95 (mt, 1H×0.25: 1'$H_6$ 2nd isomer).

5γ-Deoxy-5γ-hydroxyiminopristinamycin $I_A$ can be obtained by stirring pristinamycin $I_A$ (15 g) and hydroxylamine hydrochloride (7.5 g) dissolved in methanol (150 cc) containing a 2N methanolic solution (8 cc) of hydrogen chloride gas for 5 hours at a temperature of about 20° C. The reaction mixture is then concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. The residue is triturated with a mixture of chloroform (100 cc) and of a saturated aqueous solution of sodium bicarbonate (100 cc); the organic phase is separated off and the aqueous phase is extracted twice with chloroform (200 cc in total). The organic phases are combined, dried over magnesium sulphate, filtered, and concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. In this manner, 5γ-deoxy-5γ-hydroxyiminopristinamycin $I_A$ (14 g) is obtained in the form of a beige powder melting at 210° C.

NMR spectrum: 0.35 (dd, 1H: $5\beta_2$), 3.25 (m, 2H: $4\epsilon_2+5\beta_1$), 5.05 (d, 1H: 5α), 5.5 (m, 2H including $5\epsilon_1$), 7.80 (dd, 1H×0.40: 1'$H_6$ 1st isomer), 7.90 (dd, 1H×0.60: 1'$H_6$ 2nd isomer).

Reference Example 13

By using a method similar to that described in reference Example 11, 5γ-[N-(carboxymethyl)methylamino]-5γ-deoxypristinamycin $I_A$ (0.8 g) is obtained in the form of a cream-coloured powder melting at about 140° C.

An aqueous solution at a concentration of 2% of 5γ-[N-(carboxymethyl)methylamino]-5γ-deoxypristinamycin $I_A$ (product K) is obtained with:

| | |
|---|---|
| product K | 0.2 g |
| distilled water q.s. | 10 cc |

Reference Example 14

Acetyl chloride (0.3 cc) is added to a solution of 5γ-deoxy-5γ-(2-dimethylaminoethyl)aminopristinamycin $I_A$ (3.2 g) in chloroform (50 cc) containing triethylamine (0.6 cc). The reaction mixture is stirred at a temperature of about 20° C. for 30 minutes and is then concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. The residue is purified by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)]; by concentrating fractions 10 to 21 to dryness under reduced pressure (2.7 kPa) at 30° C., 5γ-deoxy-5γ-[N-(2-dimethylaminoethyl)acetamido]pristinamycin $I_A$ (1.8 g) is obtained in the form of a white powder melting at about 170° C.

NMR spectrum: 0.9 (m, 4H: $2\gamma+5\beta_2$), 2.05 to 2.15 (m, 3H: $5\delta_1+5\delta_2+5\gamma$), 2.15 (S, 3H: $-COCH_3$), 2.45 (s, 6H: $-N(CH_3)_2$), 2.35 to 2.60 (m, 5H: $>N-\underline{CH_2}-\underline{CH}_2-N<+5\beta_1$), 7.8 (mt, 1H×0.75: 1'$H_6$ 1st isomer), 8.25 (mt, 1H×0.25: 1'$H_6$ 2nd isomer).

An aqueous solution at a concentration of 10% of 5γ-deoxy-5γ-[N-(2-dimethylaminoethyl)acetamido]-pristinamycin $I_A$ (product L), in the form of hydrochloride, is obtained with:

| | |
|---|---|
| product L | 0.1 g |
| 0.2 N hydrochloric acid | 0.51 cc |
| distilled water q.s. | 1 cc |

5γ-Deoxy-5γ-(2-dimethylaminoethyl)aminopristinamycin $I_A$ can be prepared as described in Reference Example 2.

Reference Example 15

By using a method similar to that described in Reference Example 14, 5γ-deoxy-5γ-[N-(3-dimethylaminopropyl)acetamido]pristinamycin $I_A$ (1.6 g) is obtained in the form of an ochre powder melting at 210° C.

An aqueous solution at a concentration of 10% of 5γ-deoxy-5γ-[N-(3-dimethylaminopropyl)acetamido]-pristinamycin $I_A$ (product M), in the form of hydrochloride, is obtained.

Reference Example 16

3-Dimethylaminopropanethiol (1.95 g) is added to a solution of 5δ-methylenepristinamycin $I_A$ (3.6 g) in a mixture of methanol (25 cc) and chloroform (5 cc), and then the solution obtained is stirred at a temperature of about 20° C. for 20 hours. The reaction mixture is then poured into distilled water (250 cc); the emulsion obtained is extracted 3 times with methylene chloride (250 cc in total). The organic phases are combined, dried over magnesium sulphate, filtered, and then concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. The residue obtained is purified by "flash" chromatography [eluent: chloroform-methanol (95-5 by volume)]; fractions 10 to 38 are concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. The residue obtained is triturated in ethyl ether (30 cc); the crystals obtained are separated off by filtration, and then dried under reduced pressure (27 Pa) at 20° C. In this manner, 5δ-(3-dimethylaminopropyl)thiomethylpristinamycin $I_A$ is obtained in the form of white crystals melting at 234° C.

NMR spectrum:

| δ (ppm) | | Form | Attribution |
|---|---|---|---|
| 11.65 | | s (broad) | OH |
| 8.70 | | d | 6NH |
| 8.40 | | d | 1NH |
| 7.80 | | dd | 1'$H_6$ |
| 7.45 | | m | 1'$H_4$ + 1'$H_5$ |
| 7.27 | | m | 6γ + 6δ + 6ε |
| 7.17 | | m | |
| 7.05 | d | AB system | 4δ + 4ε |
| 6.60 | d | | |
| 6.47 | | d | 2 NH |
| 5.87 | | ddd | 1β |
| 5.83 | | d | 6α |
| 5.24 | | m | 5α + 4α |
| 5.03 | | ddd | $5\epsilon_1$ |
| 4.85 | | dd | 1α |
| 4.80 | | m | 2α |
| 4.53 | | dd | 3α |
| 3.53 | | m | $3\delta_1$ |
| 3.35 | dd | ABX system | $-\underline{CH_2}-S-SCH_2-$ |
| 3.15 | dd | | |
| 3.25 | | s | 4 $NCH_3$ |
| 3.25 | | m | $3\delta_2$ |
| 2.90 | | s | 4-$N(CH_3)_2$ |
| 2.90 | | m | 4β |
| 2.55 | | t | $-\underline{CH_2}N(CH_3)_2$ |
| 2.50 | | dd | $5\epsilon_2$ |
| 2.40 | | t | $-CH_2S\underline{CH_2}-$ |
| 2.40 to 2.20 | | m | $5\delta + 5\beta_1$ |
| 2.25 | | s | $-CH_2N(\underline{CH_3})_2$ |
| 2 | | m | $3\beta_1$ |
| 1.75 | | m | $-SCH_2\underline{CH_2}CH_2-$ |
| 1.8 to 1.45 | | m | $2\beta_1 + 2\beta_2 + 3\gamma_1$ |
| 1.30 | | d | 1γ |
| 1.25 to 1.05 | | m | $3\gamma_2 + 3\beta_2$ |
| 0.9 | | t | 2γ |
| 0.60 | | dd | $5\beta_2$ |

An aqueous solution at a concentration of 10% of 5δ-(3-dimethylaminopropyl)thiomethylpristinamycin $I_A$ (product AA) is obtained with:

| | |
|---|---|
| product AA | 30 mg |
| 0.1 N hydrochloric acid q.s. | 0.3 cc |

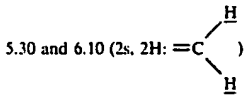
5δ-methylenepristinamycin $I_A$ can be prepared as follows:

Sodium cyanoborohydride (0.43 g) is added to a solution of 5δ-dimethylaminomethylenepristinamycin $I_A$ (12 g) in tetrahydrofuran (230 cc) containing trifluoroacetic acid (1.2 cc). The solution obtained is stirred at a temperature of about 20° C. for 4 hours and is then concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. The residue obtained is purified by "flash" chromatography [eluent: chloroform-methanol (95-5 by volume)]; fractions 4 to 15 are concentrated to dryness

under reduced pressure (2.7 kpa) at 30° C. In this manner 5δ-methylenepristinamycin $I_A$ (5.5 g) is obtained in the form of white crystals melting at 245° C.

NMR spectrum:

0.55 (d, 1H: $5\beta_2$)
2.40 (d, 1H: $5\beta_1$)
3.55 (dd, 1H: $5\epsilon_2$)
5.25 (m, 2H: $5\alpha + 5\epsilon_1$)




7.85 (dd, 1H: $1'H_6$)

5δ-Dimethylaminomethylenepristinamycin $I_A$ can be prepared as follows:

tert-Butoxybis(dimethylamino)methane (230 cc) is added to a solution of pristinamycin $I_A$ (46 g) in 1,2-dichloroethane (460 cc); the solution obtained is stirred at a temperature of about 20° C. for 18 hours. The reaction mixture is diluted with methylene chloride (1 liter) and then washed 3 times with a 0.4% strength aqueous solution of ammonium chloride (3 liters in total). The organic phase is dried over magnesium sulphate, filtered and then concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. The residue obtained is triturated with distilled water (600 cc); the mixture is filtered and the solid product is dried under reduced pressure (2.7 kPa) at 20° C. Crude 5δ-dimethylaminomethylenepristinamycin $I_A$ (41 g) is obtained in the form of a beige powder. This product is of an adequate quality to be used as such as in the subsequent steps. It can, however, be purified as follows:

Crude 5δ-dimethylaminomethylelenpristinamycin $I_A$ (23.5 g) is purified by "flash" chromatography [eluent: chloroform-methanol (98-2 by volume)]. Fractions 16 to 25 are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. In this manner, 5δ-dimethylaminomethylenepristinamycin $I_A$ (12 g) is obtained in the form of a beige powder melting at about 195° C.

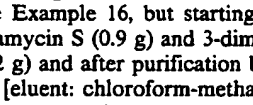
NMR spectrum: 0.9 (t, 3H: $2\gamma$), 1.0 (dd, 1H: $5\beta_2$), 2.50 (d, 1H, $5\beta_1$), 3.10 (s, 6H: $-N(CH_3)_2$), 3.70 (d, 1H: $5\epsilon_2$), 5.50 (d, 1H: $5\epsilon_1$), 7.40 (s, 1H: $=C\underline{H}N(CH_3)_2$), 7.75 (dd, 1H: $1'H_6$).

## Reference Example 17

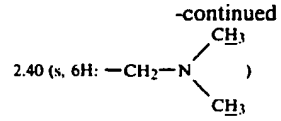
By using a method similar to that described in Reference Example 16, but starting from 5δ-methylenevirginiamycin S (0.9 g) and 3-dimethylaminopropanethiol (0.52 g) and after purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)], and concentrating fractions 13 to 25 to dryness under reduced pressure (2.7 kPa) at 30° C., 5δ-(3-dimethylaminopropyl)thiomethylvirginiamycin S (0.3 g) is obtained in the form of a white powder melting at about 142° C.

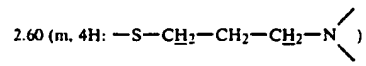
NMR spectrum:

0.45 (dd, 1H: $5\beta_2$)




-continued




3.45 (d, 1H: $5\epsilon_2$)

4.85 (m, 3H including $5\epsilon_1$)

5.25 (dd, 1H: $5\alpha$)

7.78 (dd, 1H: $1'H_6$)

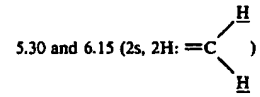
An aqueous solution at a concentration of 10% of 5δ-(3-dimethylaminopropyl)thiomethylviginiamycin S (product AB), in the form of hydrochloride, is obtained with:

| | |
|---|---|
| product AB | 0.1 g |
| hydrochloric acid q.s. | 1 cc |

5δ-Methylenevirginiamycin S can be prepared by a method similar to that described in Reference Example 16 for 5δ-methylenepristinamycin $I_A$, but starting from 5δ-dimethylaminomethylenevirginiamycin S (2 g) and sodium cyanoborohydride (74 mg). After purification by "flash" chromatography [eluent: chloroform-methanol (98-2 by volume)] and concentrating fractions 2 to 5 to dryness under reduced pressure (2.7 kPa) at 30° C., 5δ-methylenevirginiamycin S (1 g) is obtained in the form of a beige powder melting at about 190° C.

NMR spectrum:

0.35 (dd, 1H: $5\beta_2$)
2.45 (dd, 1H: $5\beta_1$)
3.55 (dd, 1H: $5\epsilon_2$)
5.25 (dd, 1H: $5\epsilon_1$)
5.25 (m, 1H: $5\alpha$)




7.75 (dd, 1: $1'H_6$)

5δ-Dimethylaminomethylenevirginiamycin S can be obtained by using a method similar to that described in Reference Example 16 for 5δ-dimethylaminomethylenepristinamycin $I_A$, but starting from virginiamycin S (2 g) and bis(dimethylamino)tert-butoxymethane (10 cc) and, after purification by "flash" chromatography [eluent: chloroform-methanol (98-2 by volume)] and concentrating fractions 9 to 12 to dryness under reduced pressure (2.7 kPa) at 30° C., 5δ-dimethylaminomethylenevirginiamycin S (0.8 g) is obtained in the form of a yellow powder melting at about 175° C.

NMR spectrum: 0.9 (m, 4H: $2\gamma+5\beta_2$), 3.05 (s, 6H: $=CH-N(C\underline{H}_3)_2$), 3.65 (d, 1H: $5\epsilon_2$), 4.85 (d, 1H: $5\epsilon_1$), 5.15 (dd, 1H: $5\alpha$), 7.10 to 7.40 (m: aromatics+$=C\underline{H}-N<$), 7.70 (dd, 1H: $1'H_6$). Reference Example 18

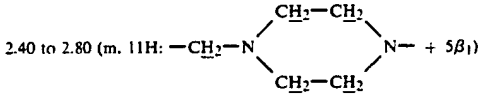
By using a method similar to that described in Reference Example 16, but starting from 5δ-methylenepristinamycin $I_A$ (6 g) and 2-(4-methylpiperazinyl)ethane-

thiol (4 cc), and after purification by "flash" chromatography [eluent: chloroform-methanol (97-3 by volume)], and concentrating fractions 8 to 20 to dryness under reduced pressure (2.7 pKa) at 30° C., 5δ-[2-(4-methylpiperazinyl)ethyl]thiomethylpristinamycin $I_A$ (2.6 g) is obtained in the form of white crystals melting at 216° C.

NMR spectrum:

0.60 (dd, 1H: $5\beta_2$)

2.27 (s, 3H:  )

2.40 to 2.80 (m, 11H:  )

5.05 (dd, 1H: $5\epsilon_1$)
5.27 (m, 2H: $5\alpha + 4\alpha$)
7.85 (mt, 1H × 0.8: $1'H_6$ 1st isomer)
7.95 (mt, 1H × 0.2: $1'H_6$ 2nd isomer)

An aqueous solution at a concentration of 5% of 5δ-[2-(4-methyl-1-piperazinyl)ethyl]thiomethylpristinamycin $I_A$ (product AC), in the form of hydrochloride, is obtained with:

| | |
|---|---|
| product AC | 0.1 g |
| 0.1 N hydrochloric acid | 0.96 cc |
| distilled water q.s. | 2 cc |

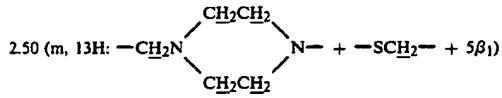
## Reference Example 19

By using a method similar to that described in reference Example 16, but starting from 5δ-methylenepristinamycin $I_A$ (2 g) and 3-(4-methyl-1-piperazinyl)-propanethiol (3 cc), and after purification by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)], and concentrating fractions 10 to 25 to dryness under reduced pressure (2.7 pKa) at 30° C., 5δ-[3-(4-methyl-1-piperazinyl)propyl]thiomethylpristinamycin $I_A$ (1.9 g) is obtained in the form of a white powder melting at about 156° C.

NMR spectrum:

0.65 (dd, 1H: $5\beta_2$)

2.30 (s, 3H:  )

2.50 (m, 13H:  )

5.27 (m, 2H: $5\alpha + 4\alpha$)
7.85 (dd, 1H × 0.8: $1'H_6$ 1st isomer)
7.95 (dd, 1H × 0.2: $1'H_6$ 2nd isomer)

An aqueous solution at a concentration of 10% of 5δ-[3-(4-methyl-1-piperazinyl)propyl]thiomethylpristinamycin $I_A$ (product AD), in the form of hydrochloride, is obtained with:

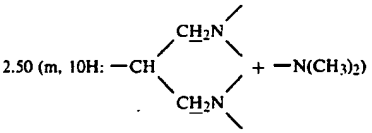
| | |
|---|---|
| product AD | 0.1 g |
| 0.5 N hydrochloric acid | 0.38 cc |
| distilled water q.s. | 1 cc |

## Reference Example 20

By using a method similar to that described in Reference Example 16, but starting from 5δ-methylenepristinamycin $I_A$ (4 g) and 1,3-bisdimethylamino-2-propanethiol (4 cc), and after purification by "flash" chromatography [eluent: chloroform-methanol (95-5 by volume)], and concentrating fractions 20 to 60 to dryness under reduced pressure (2.7 kPa) at 30° C., 5δ-[1,3-bis(dimethylamino)-2-propyl]thiomethylpristinamycin $I_A$ (0.59 g) is obtained in the form of a white powder melting at about 170° C.

NMR spectrum:

0.63 (dd, 1H: $5\beta_2$)
2.40 (s, 6H: $-N(CH_3)_2$)

2.50 (m, 10H:  )

4.97 (s, 1H: $5\epsilon_1$)
5.30 (m, 2H: $5\alpha + 4\alpha$)
7.85 (mt, 1H × 0.85: $1'H_6$ 1st isomer)
7.95 (mt, 1H × 0.15: $1'H_6$ 2nd isomer)

An aqueous solution at a concentration of 7.5% of 5δ-[1,3-bis(dimethylamino)-2-propyl]thiomethylpristinamycin $I_A$ (product AE), in the form of hydrochloride, is obtained with:

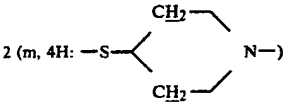
| | |
|---|---|
| product AE | 0.03 g |
| 0.1 N hydrochloric acid | 0.3 cc |
| distilled water q.s. | 0.4 cc |

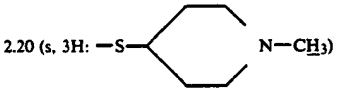
## Reference Example 21

By using a method similar to that described in reference Example 16, but starting from 5δ-methylenepristinamycin $I_A$ (3 g) and 2-methyl-4-mercaptopiperidine (0.97 g), and after purification by "flash" chromatography [eluent: chloroform-methanol (95-5 by volume)], and concentrating fractions 10 to 16 to dryness under reduced pressure (2.7 kPa) at 30° C., 5δ-(1-methyl-4-piperidyl)thiomethylpristinamycin $I_A$ (1.1 g) is obtained in the form of a white powder melting at 260° C.

NMR spectrum:

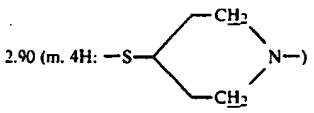
0.6 (dd, 1H: $5\beta_2$)

2 (m, 4H:  )

2.20 (s, 3H:  )

-continued

2.35 (m, 1H: 5$\beta_1$)



2.90 (m, 4H: —S— CH2 N— CH2)

5.30 (m, 2H: 5$\alpha$ + 4$\alpha$)
7.85 (dd, 1H: 1'$H_6$)

An aqueous solution at a concentration of 5% of 5δ-(1-methyl-4-piperidyl)thiomethylpristinamycin $I_A$ (product AF), in the form of hydrochloride, is obtained with:

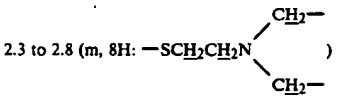
| | |
|---|---|
| product AF | 0.03 g |
| 0.1 N hydrochloric acid | 0.3 cc |
| distilled water q.s. | 0.6 cc |

## Reference Example 22

By repeating Reference Example 16, but starting from 5δ-methylenepristinamycin $I_A$ (2 g) and 2-diethylaminoethanethiol (0.66 g), after purification by "flash" chromatography [eluent: chloroform-methanol (95-5 by volume)], and concentrating fractions 9 to 18 to dryness under reduced pressure (2.7 kPa) at 30° C., 5δ-(2-diethylaminoethyl)thiomethylpristinamycin $I_A$ (0.8 g) is obtained in the form of a beige powder melting at 230° C.

NMR spectrum:

0.65 (dd, 1H: 5$\beta_2$)
2.38 (d, 1H: 5$\beta_1$)



2.3 to 2.8 (m, 8H: —SCH2CH2N(CH2—)(CH2—))

3.15 (dd, 1H: —CH2S—)
3.35 (dd, 1H: —CH2S—)
5.01 (dd, 1H: 5$\epsilon_1$)
7.81 (dd, 1H × 0.9: 1'$H_6$ 1st isomer)
7.90 (dd, 1H × 0.1: 1'$H_6$ 2nd isomer)

An aqueous solution at a concentration of 5% of 5δ-(2-diethylaminoethyl)thiomethylpristinamycin $I_A$ (product $AF_1$) in the form of hydrochloride, is obtained with:

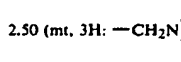
| | |
|---|---|
| product $AF_1$ | 30 mg |
| 0.1 N hydrochloric acid | 0.29 cc |
| distilled water q.s. | 0.6 cc |

## Reference Example 23

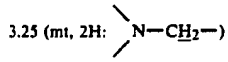
2-Dimethylaminoethylamine (5.3 g) is added dropwise, so as not to exceed 25° C., to a solution of 5δ-dimethylaminomethylenepristinamycin $I_A$ (5.5 g) in acetic acid (60 cc). The solution obtained is stirred at a temperature of about 20° C. for 20 hours and is then poured slowly into a saturated aqueous solution of sodium bicarbonate; the mixture obtained is extracted twice with methylene chloride (750 cc in total). The organic phases are combined, dried over magnesium sulphate, filtered, and concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. The residue is purified by "flash" chromatography [eluent: chloroform-methanol (90-10 by volume)]; fractions 10 to 12 are concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. In this manner 5δ-(2-dimethylaminoethyl-)aminomethylenepristinamycin $I_A$ (3 g) is obtained in the form of a beige powder melting at about 180° C.

NMR spectrum:

0.90 (mt, 4H: 2$\gamma$ + 5$\beta_2$)
2.25 (mt, 6H: —N(CH3)2)

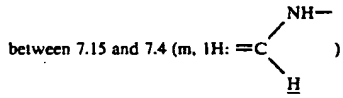


2.50 (mt, 3H: —CH2N< + 5$\beta_1$)



3.25 (mt, 2H: >N—CH2—)

3.50 (mt, 2H: 5$\epsilon_2$ + 3$\delta_1$)
4.90 (mt, 1H: 5$\epsilon_1$)



between 7.15 and 7.4 (m, 1H: =C(NH—)(H) )

9.90 (mt, 1H (exchangeable with $D_2O$): —NH—)

An aqueous solution at a concentration of 1% of 5δ-(2-dimethylaminoethyl)aminomethylenepristinamycin $I_A$ (product AG) is obtained with:

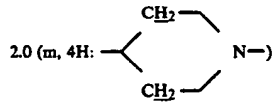
| | |
|---|---|
| product AG | 0.1 g |
| distilled water q.s. | 10 cc |

## Reference Example 24

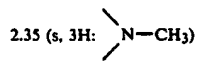
By using a method similar to that described in Reference Example 23, but starting from 5δ-dimethylaminomethylenepristinamycin $I_A$ (13.8 g) and 4-amino-2-methylpiperidine (3.4 g), and after purification by "flash" chromatography [eluent: chloroform-methanol (92.5-7.5 by volume)], and concentrating fractions 15 to 20 to dryness under reduced pressure (2.7 kPa) at 30° C., 5δ-(1-methyl-4-piperidyl)aminomethylenepristinamycin $I_A$ (4.0 g) is obtained in the form of a yellow powder melting at 208° C.

NMR spectrum:

0.40 (m, 4H: 2$\gamma$ + 2$\beta_2$)



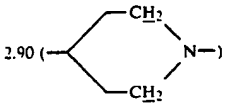
2.0 (m, 4H: CH2 N— CH2)



2.35 (s, 3H: >N—CH3)

2.45 (d, 1H: 5$\beta_1$)

-continued

2.90 (  )

3.20 (under unresolved bands. 1H: —CH  N—)

3.50 (d. 1H: $5\epsilon_2$)
4.85 (under unresolved bands. 1H: $5\epsilon_1$)
6.65 (d. 1H: =CHNH—)
9.70 (dd. 1H × 0.15: =CH—NH— 1st isomer)
10.03 (dd. 1H × 0.85: =CH—NH— 2nd isomer)

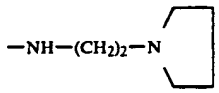
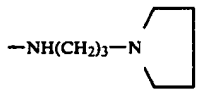
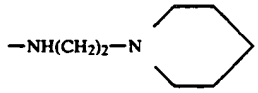
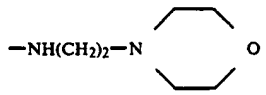
An aqueous solution at a concentration of 10% of 5δ-(1-methyl-4-piperidyl)aminomethylenepristinamycin $I_A$ (product AT), in the form of hydrochloride, is obtained with:

| | |
|---|---|
| product AT | 0.03 g |
| 0.1 N hydrochloric acid | 0.3 cc |
| distilled water q.s. | 0.3 cc |

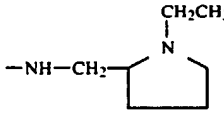
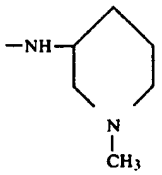
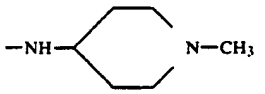
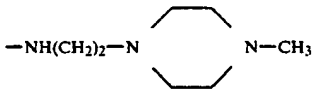
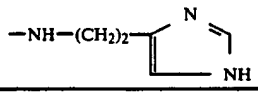
4-Amino-2-methylpiperidine can be prepared by the method described by E. F. Elslager, L. M. Werbel, A. Curry, N. Headen, J. Johnson, J. Med. Chem. 17, 99 (1974).

By using the method of Reference Example 23, the following synergistins of general formula (V), which can be combined with the products according to the invention, are prepared.

[The symbols =====, X and Z are defined as at 2b) for the general formula (V) and, unless stated otherwise, Y denotes a dimethylamino radical].

| Reference example | Y | $R_4$ | (1) Melting point<br>(2) Solubility |
|---|---|---|---|
| 25 | | $-NH-(CH_2)_2N(C_2H_5)_2$ | (1) Yellow powder M abt. 150° C.<br>(2) 5% aqueous solution as hydrochloride |
| 26 | | $-NH(CH_2)_2NHCH_3$ | (1) Yellow powder M = 174° C.<br>(2) 1% aqueous solution as hydrochloride |
| 27 | | $-NH(CH_2)_3N(CH_3)_2$ | (1) Yellow powder M abt. 155° C.<br>(2) 6.6% aqueous solution as hydrochloride |
| 28 | | $-NH-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-CH_2N(CH_3)_2$ | (1) Yellow powder M abt. 160° C.<br>(2) 1% aqueous solution as hydrochloride |
| 29 | | $-NHCH_2\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-N(CH_3)_2$ | (1) Orange powder M abt. 175° C.<br>(2) 10% aqueous solution as hydrochloride |
| 30 | | $-NH-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-(CH_2)_3N(C_2H_5)_2$ | (1) Beige powder M abt. 160° C.<br>(2) 1% aqueous solution as hydrochloride |
| 31 | |  | (1) Yellow powder M = 183° C.<br>(2) 1% aqueous solution as hydrochloride |
| 32 | |  | (1) Yellow powder M = 170° C.<br>(2) 1% aqueous solution |
| 33 | |  | (1) Yellow powder M = 162° C.<br>(2) 1% aqueous solution as hydrochloride |
| 34 | |  | (1) Beige powder M abt. 172° C.<br>(2) 1% aqueous solution as hydrochloride |

-continued

| Reference example | Y | $R_4$ | (1) Melting point (2) Solubility |
|---|---|---|---|
| 35 | |  | (1) Beige powder M abt. 160° C. (2) 1% aqueous solution as hydrochloride |
| 36 | |  | (1) Beige powder M = 177° C. (2) 1% aqueous solution as hydrochloride |
| 37 | H |  | (1) Beige powder M abt. 195° C. (2) 5% aqueous solution as hydrochloride |
| 38 | $-N(CH_3)_2$ |  | (1) Yellow powder M = 150° C. (2) 10% aqueous solution as hydrochloride |
| 39 | $-N(CH_3)_2$ |  | (1) Yellow powder M = 138° C. (2) 10% aqueous solution as hydrochloride |

Reference Example 40

2-Dimethylaminoethanethiol (2.1 g) is added to a solution of 5δ-dimethylaminomethylenepristinamycin $I_A$ (1.84 g) in acetic acid (40 cc). The solution obtained is stirred at a temperature of about 20° C. for 20 hours and is then poured slowly into a saturated aqueous solution of sodium bicarbonate; the mixture obtained is extracted 3 times with methylene chloride (400 cc in total). The organic phases are combined, dried over magnesium sulphate, filtered, and concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. The residue obtained is purified by "flash" chromatography [eluent: chloroform-methanol (96-4 by volume)]; fractions 5 and 6 are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. In this manner, 5δ-(2-dimethylaminoethyl)thiomethylenepristinamycin $I_A$ (0.8 g) is obtained in the form of a yellow powder melting at about 150° C.

NMR spectrum: 0.68 (dd, 1H: $5\beta_2$), 2.32 (s, 6H×0.85: $-CH_2N(C\underline{H}_3)_2$ 1st isomer), 2.35 (s, 6H×0.15: $-CH_2N(C\underline{H}_2$ 2nd isomer), 2.45 (d, 1H: $5\beta_1$), 2.65 (mt, 2H: $-SC\underline{H}_2-$), 3.05 (t, 2H: $-C\underline{H}_2N<$), 3.43 (dd, 1H: $5\epsilon_2$), 5.15 (in unresolved bands: $5\epsilon_1$), 7.60 (broad s, 1H: $=C\underline{H}S-$), 7.83 (mt, 1H: $1'H_6$, two isomers).

An aqueous solution at a concentration of 1% of 5δ-(2-dimethylaminoethyl)thiomethylenepristinamycin $I_A$ (product AX), in the form of hydrochloride, is obtained with:

| | |
|---|---|
| product AX | 0.1 g |
| 0.1 N hydrochloric acid | 1 cc |
| distilled water q.s. | 10 cc |

By using the method of reference Example 40, the following synergistins of general formula (V) which can be combined with the products according to the invention, are prepared.

[The symbols ===== , X and Z are defined as in (2b) for the general formula (V), and, unless mentioned otherwise, Y denotes a dimethylamino radical].

| Reference example | Y | $R_4$ | (1) Melting point (2) Solubility |
|---|---|---|---|
| 41 | $-N(CH_3)_2$ | $-S-(CH_2)_2N(C_2H_5)_2$ | (1) Beige powder M abt. 192° C. (2) 1% aqueous solution as hydrochloride |
| 42 | $-N(CH_3)_2$ | $-S-(CH_2)_3N(CH_3)_2$ | (1) Beige powder M abt. 170° C. (2) 1% aqueous solution as hydrochloride |
| 43 | —H | $-S(CH_2)_3N(CH_3)_2$ | (1) Beige powder M abt. 140° C. (2) 10% aqueous solution as hydrochloride |

-continued

| Reference example | Y | $R_4$ | (1) Melting point (2) Solubility |
|---|---|---|---|
| 44 | $-N(CH_3)_2$ | $-S\ CH_2-CH(CH_3)-CH_2N(CH_3)_2$ | (1) Beige powder M = 234° C. (2) 10% aqueous solution as hydrochloride |
| 45 | $-N(CH_3)_2$ | $-S-CH_2-C(CH_3)_2-N(CH_3)_2$ | (1) Beige powder M abt. 200° C. (2) 1% aqueous solution as hydrochloride |
| 46 | $-N(CH_3)_2$ | $-S(CH_2)_2-N$ (pyrrolidine) | (1) Beige powder M abt. 180° C. (2) 1% aqueous solution as hydrochloride |
| 47 | | $-S-(CH_2)_2-$(2-(1-methylpyrrolidinyl)) | (1) Beige powder M abt. 215° C. (2) 0.6% aqueous solution as hydrochloride |
| 48 | | $-S-$(4-methylpiperazinyl) | (1) Yellow powder M abt. 170° C. (2) 1% aqueous solution as hydrochloride |
| 49 | | $-S-$(4-ethylpiperazinyl) | (1) Beige powder M abt. 175° C. (2) 1% aqueous solution as hydrochloride |
| 50 | | $-S-(CH_2)_2N(CH_3)-(CH_2)_2N(CH_3)_2$ | (1) Yellow powder M abt. 160° C. (2) 1% aqueous solution |
| 51 | | $-S-CH[CH_2N(CH_3)_2]_2$ | (1) Beige powder M abt. 190° C. (2) 1% aqueous solution as hydrochloride |
| 52 | | $-S(CH_2)_2-N$ (4-methylpiperazinyl) | (1) Beige powder M abt. 170° C. (2) 1% aqueous solution as hydrochloride |
| 53 | | $-S(CH_2)_3-N$ (4-methylpiperazinyl) | (1) Beige powder M abt. 190° C. (2) 10% aqueous solution as hydrochloride |
| 54 | | $-S-CH_2-CH(CH_3)-CH_2-N^{\oplus}(CH_3)_3$ | (1) Ochre powder M abt. 150° C. (2) 1% aqueous solution as hydrochloride |
| 55 | | $-S(CH_2)_2SO_3H$ | (1) Yellow powder M > 280° C. (2) 5% aqueous solution |

Reference Example 56

A solution of 5δ-(4-methylphenyl)sulphonyloxymethylenepristinamycin $I_A$ (5.2 g) in methylene chloride (50 cc) is added to a solution of 1-(2-mercaptopropyl)-4-methylpiperazine (0.87 g) in ethanol (50 cc), to which sodium ethoxide (0.34 g) has been added. The reaction mixture is stirred at a temperature of about 20° C. for 16 hours and is then diluted with methylene chloride (500 cc) and distilled water (100 cc). After stirring, the aqueous phase is extracted twice with methylene chloride (50 cc in total). The organic phases are combined, dried over magnesium sulphate, filtered, and then concen-

trated to dryness under reduced pressure (2.7 pKa) at 30° C. The residue is purified by "flash" chromatography [eluent: chloroform-methanol (97.5-2.5 by volume)]. Fractions 33 to 80 are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. In this manner, 5δ-[3-(4-methyl-1-piperazinyl)-2-propyl]thiomethylenepristinamycin $I_A$ (1.25 g) is obtained in the form of a beige powder melting at about 195° C.

NMR spectrum:

0.70 (dd, 1H: $5\beta_2$)

1.25 (d, 3H: $-\underset{|}{C}H-C\underline{H}_3$)

2.30 (s, 3H: $N-C\underline{H}_3$)

2.50 (m, 10H: $-C\underline{H}_2-N$, $N-C\underline{H}_3$, $C\underline{H}_2C\underline{H}_2$)

3.40 (dd, 1H: $5\epsilon_2$)
7.85 (broad dd, 1H: $1'H_6$)

An aqueous solution at a concentration of 10% of 5δ-[3-(4-methyl-1-piperazinyl)-2-propyl]thiomethylenepristinamycin $I_A$ (product AAN) in the form of hydrochloride is obtained with:

| | |
|---|---|
| product AAN | 0.03 g |
| 0.1 N hydrochloric acid | 0.3 cc |

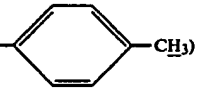
1-(2-Mercaptopropyl)-4-methylpiperazine is prepared by heating a mixture of propylene sulphide (19 cc) and N-methylpiperazine (29 cc) at 100° C. for 16 hours. In this manner, a colourless oil (32 g) which distils at 105° C. at 1.3 kPa is obtained.

5δ-(4-Methylphenyl)sulphonyloxymethylenepristinamycin $I_A$ can be obtained as follows:

Triethylamine (0.42 cc), and then p-toluenesulphonyl chloride (0.57 g) are added to a solution of 5δ-hydroxymethylenepristinamycin $I_A$ (2.7 g) in methylene chloride (30 cc), at a temperature of about −30° C. The reaction mixture is then stirred at a temperature of about 20° C. for 2 hours and is then concentrated to dryness under reduced pressure (2.7 kPa) at 30° C.; the residue obtained is purified by "flash" chromatography [eluent: methylene chloride-methanol (96-4 by volume)]. After concentrating fractions 4 to 6 to dryness under reduced pressure (2.7 kPa) at 30° C., 5δ-(4-methylphenyl)sulphonyloxymethylenepristinamycin $I_A$ (2.2 g) is obtained in the form of a white powder melting at about 265° C.

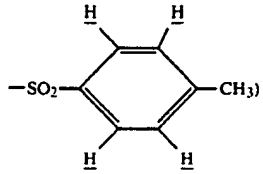
NMR spectrum:

0.50 (dd, 1H: $5\beta_2$)

2.35 (s, 3H: $-SO_2-$  $-C\underline{H}_3$)

3.30 (dd, 1H: $5\epsilon_2$)

-continued

5.25 (d, 1H: $5\alpha$)
5.30 (dd, 1H: $5\epsilon_1$)
7.35 to 7.90 (AB system + m, 8H: $4\delta + 4\epsilon +$  )

7.85 (dd, 1H: $1'H_6$)

5δ-Hydroxymethylenepristinamycin $I_A$ can be prepared as follows:

5δ-Dimethylaminomethylenepristinamycin $I_A$ (10.6 g) is added to a 0.1N aqueous solution (420 cc) of hydrochloric acid. The solution obtained is then stirred at a temperature of about 20° C. for 3 hours. A saturated aqueous solution (30 cc) of sodium bicarbonate is then added dropwise so as to produce a pH of about 4. The product which precipitates is separated off by filtration and is then washed 3 times with distilled water (30 cc in total). After drying under reduced pressure (2.7 kPa) at a temperature of about 20° C., 5δ-hydroxymethylenepristinamycin $I_A$ (9.5 g) is obtained in the form of a beige powder. This product is of adequate quality to be used as such in the subsequent steps. It can, however, be purified as follows:

Crude 5δ-hydroxymethylenepristinamycin $I_A$ (9.5 g) is dissolved in ethyl acetate (50 cc); the solution obtained is poured onto silica gel (100 g) contained in a column 2.8 cm in diameter. Ethyl acetate (400 cc) is used for the initial elution, and the corresponding eluate is discarded; elution is then continued with ethyl acetate (1600 cc), and the corresponding eluate is concentrated to dryness under reduced pressure (2.7 kPa) at 30° C. In this manner 5δ-hydroxymethylenepristinamycin $I_A$ (6.3 g) is obtained in the form of white crystals melting at 220° C.

NMR spectrum: 0.69 (dd, 1H: $5\beta_2$), 2.43 (d, 1H: $5\beta_1$), 3.40 (d, 1H: $5\epsilon_2$), 4.0 to 4.2 (m, 3H: $4\alpha+5\epsilon_1+5\alpha$), 8.15 (s, 1H: $=C\underline{H}-OH$), 11.63 (broad s, 1H: $=CH-O\underline{H}$).

## Reference Example 57

By using a method similar to that described in Reference Example 56, 5δ-(3-dimethylamino-2-propyl)thiomethylenepristinamycin $I_A$ (1 g) is obtained in the form of a yellow powder melting at 172° C.

An aqueous solution at a concentration of 5% of 5ε-(3-dimethylamino-2-propyl)thiomethylenepristinamycin $I_A$, in the form of hydroxychloride, is obtained.

## Reference Example 58

By using a method similar to that described in Reference Example 56, 5δ-(5-diethylamino-2-pentyl)thiomethylenepristinamycin $I_A$ (1.32 g) is obtained in the form of a beige powder melting at about 185° C.

An aqueous solution at a concentration of 10% of 5δ-(5-diethylamino-2-pentyl)thiomethylenepristinamycin $I_A$ in the form of hydrochloride, is obtained.

## Reference Example 59

A solution of 5δ-[(4-methylphenyl)sulphonyloxymethylene]pristinamycin $I_A$ (7.6 g) in tetrahydrofuran (60 cc) is cooled to a temperature of about −10° C. While

maintaining this temperature, a solution is added to it, consisting of 2-dimethylaminoethanol (0.65 g) in tetrahydrofuran (60 cc), to which a 50% strength dispersion (0.35 g) of sodium hydride in mineral oil has been added. When the addition is complete, the temperature is allowed to rise slowly to about 20° C. The reaction mixture is stirred at this temperature for 24 hours and is then diluted with methylene chloride (500 cc) and washed with a saturated solution of ammonium chloride (2×50 cc). The organic phase is dried over magnesium sulphate, filtered, and then concentrated to dryness under reduced pressure (2.7 kPa) at 40° C. The residue obtained is purified by "flash" chromatography [eluent: chloroformmethanol (95-5 by volume)]. Fractions 12 to 17 are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 25° C. In this manner, 5δ-(2-dimethylaminoethoxymethylene)pristinamycin $I_A$ (1.5 g) is obtained in the form of a beige powder melting at about 160° C.

NMR spectrum:

0.65 (dd, 1H: $5\beta_2$), 2.3 (s, 6H: $-N(CH_3)_2$), 2.65 (m, 2H: $-CH_2N<$), 3.42 (dd, 1H: $5\epsilon_2$), 4.15 (t, 2H: $-OCH_2-$), 5.15 (d, 1H: $5\epsilon_1$), 7.45 (under the aromatics, 1H: $>C=CHO$), 7.80 (dd, 1H: $1'H_6$).

An aqueous solution at a concentration of 1% of 5δ-(2-dimethylaminoethoxymethylene)pristinamycin $I_A$ (product AAQ), in the form of hydrochloride, is obtained with:

| | |
|---|---|
| product AAQ | 0.03 g |
| 0.1 N hydrochloric acid | 0.3 cc |
| distilled water q.s. | 3 cc |

The present invention also relates to the medications consisting of a product of general formula (I) in free form or preferably in the form of a salt of addition with a pharmaceutically acceptable acid in the form of a combination with known synergistins or preferably with synergistins of general formula (V), the combination being moreover capable of containing any other pharmaceutically compatible, inert or physiologically active, product. The medications according to the invention can be administered by parenteral, oral, rectal or topical route.

Sterile compositions for parenteral administration can be, preferably, aqueous or nonaqueous solutions, suspensions or emulsions. Water, propylene glycol, a poly(ethylene glycol), vegetable oils, especially olive oil, injectable organic esters, for example ethyl oleate, or other suitable organic solvents, can be used as a solvent or vehicle. These compositions can also contain adjuvants, especially wetting agents, isotonizing agents, emulsifiers, dispersants and stabilizers. Sterilization can be carried out in various ways, for example by an aspecticizing filtration, by adding sterilizing agents to the composition, by irradiation or by heating. They can also be prepared in the form of sterile solid compositions which can be dissolved in an injectable sterile medium at the time of use.

Tablets, pills, powders or granules can be employed as solid compositions for oral administration. In these compositions, the active product according to the invention (optionally combined with another pharmaceutically compatible product) is mixed with one or more inert diluents or adjuvants such as sucrose, lactose or starch. These compositions can also comprise substances over than diluents, for example a lubricant such as magnesium stearate.

Pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs containing inert diluents such as water or paraffin oil can be used as liquid compositions for oral administration. These compositions can also comprise substances other than the diluents, for example wetting agents, sweeteners or flavourings.

Compositions for rectal administration are suppositories or rectal capsules which contain, in addition to the active substance, excipients such as cocoa butter, semi-synthetic glycerides or poly(ethylene glycols).

Compositions for topical administration can be, for example, creams, salves, lotions, eye lotions, mouth washes, nasal drops or aerosols.

In human therapy, the products according to the invention, which are combined with known synergistins or preferably with synergistins of general formula (V), are especially useful in the treatment of infections of a microbial origin. The dosages depend on the required effect and on the duration of treatment; for an adult, they are generally between 500 and 2000 mg per day by parenteral route, especially by an intravenous route such as a slow perfusion, the dosage of synergistin of general formula (V) itself being between 500 and 2000 mg per day.

As a general rule, the practitioner will determine the dosage which he or she considers the most suitable, depending on the age, weight and all the other individual characteristics of the subject to be treated.

The following example, given without implying any limitation, illustrates the compositions according to the invention.

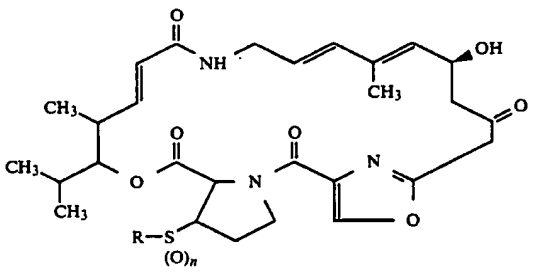
## EXAMPLE

An injectable solution for perfusion, containing 1 g/l of active mixture having the following composition is prepared:

| | |
|---|---|
| 26-(2-diethylaminoethyl)sulphinyl-pristinamycin $II_B$ | 0.6 g |
| 5δ-[2-(4-methyl-1-piperazinyl)ethyl]-thiomethylpristinamycin $I_A$ | 0.4 g |
| 0.1 N aqueous solution of hydrochloric acid | 12.7 cc |
| distilled water q.s. | 1000 cc |

We claim:

1. A pristinamycin $II_B$ of the formula:



in which R denotes

ether a 3-azetidinyl, 3-pyrrolidinyl, 3- or 4-piperidinyl or 3- or 4-azepinyl radical each of which is unsubstituted or substituted by alkyl,

or alkyl of 2 to 4 carbon atoms substituted by 1 or 2 radicals chosen from phenyl, cycloalkylamino of 3 to

6 ring atoms, N-alkyl-N-cycloalkylamino of 3 to 6 ring atoms, alkylamino, dialkylamino, and dialkylcarbamoyloxy, the alkyl moieties of the said dialkylamino and dialkylcarbamoyloxy radicals being unjoined or joined to form, with the nitrogen atom to which they are attached, and, if required, an oxygen, sulphur, or other nitrogen atom, a 1-azetidinyl, 1-pyrrolidinyl, piperidino, 1-azepinyl, morpholino, thiomorpholino in the form of sulphoxide or sulphone, 1-piperazinyl, 4-alkyl-1-piperazinyl, N-alkyl-1-homopiperazinyl or imidazolyl radical, all of which may be unsubstituted or substituted by alkyl, or R denotes an alkyl of 2 to 4 carbon atoms substituted by 2- or 3-azetidinyl, 2- or 3-pyrroliidinyl, 2-, 3- or 4-piperidyl, 2- 3- or 4-azepinyl, piperazinyl, 4-alkylpiperazinyl, quinolyl, isoquinolyl, or imidazolyl radical, each of which is unsubstituted or substituted by alkyl, these heterocyclic rings being linked to the alkyl of 2 to 4 carbon atoms by a carbon atom of the ring, n is 1 or 2 and, unless stated otherwise, the abovementioned alkyl radicals are linear or branched and contain 1 to 10 carbon atoms each, in its isomeric forms or their mixtures, or a pharmaceutically acceptable acid addition salt thereof.

2. A pristinamycin $II_B$ according to claim 1, wherein R denotes alkyl of 2 to 4 carbon atoms substituted by 1 or 2 radicals chosen from phenyl, cycloalkylamino of 5 or 6 ring atoms, N-alkyl-N-cycloalkylamino of 5 or 6 ring atoms, alkylamino of 1 to 4 carbon atoms, or dialkylamino in which each alkyl is of 1 to 3 carbon atoms or the alkyls form, with the nitrogen atom to which they are attached, a 1-azetidinyl, 1-pyrrolidinyl, piperidino, or 1-azepinyl radical, or R denotes a 3-azetidinyl, 3-pyrrolidinyl, 3- or 4-piperidyl or 3- or 4-azepinyl radical each of which is unsubstituted or substituted by alkyl of 1 to 4 carbon atoms, at least one of the substituents carried by the said alkyl being in a 1- or a 2-position, in its isomeric forms and their mixtures, or a pharmaceutically acceptable acid addition salt thereof.

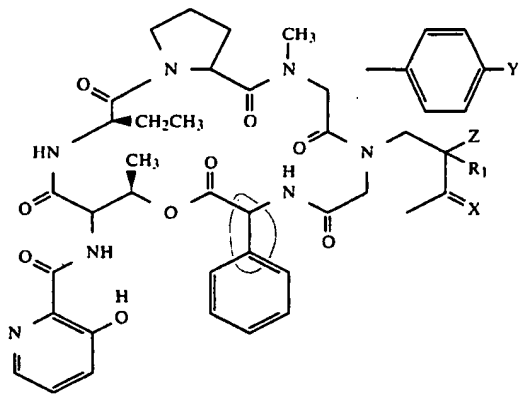
3. A pristinamycin $II_B$ according to claim 1 which is 26-(2-diethylamino-1-methylethyl)sulphinylpristinamycin $II_B$, its isomeric forms and their mixtures, or a pharmaceutically acceptable addition salt thereof.

4. A pristinamycin $II_B$ according to claim 1 which is 26-[(2R)2-dimethylaminobutyl]sulphinylpristinamycin $II_B$, its isomeric forms and their mixtures, or a pharmaceutically acceptable addition salt thereof.

5. A pristinamycin $II_B$ according to claim 1 which is 26-(2-diethylaminopropyl)sulphonylpristinamycin $II_B$, its isomeric forms and their mixtures, or a pharmaceutically acceptable acid addition salt thereof.

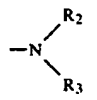
6. A pristinamycin $II_B$ according to claim 1 which is 26-(2-diisopropylaminoethyl)sulphonylpristinamycin $II_B$, its isomeric forms and their mixtures, or a pharmaceutically acceptable acid addition salt thereof.

7. A antibacterial or antimicrobial composition which contains a pristinamycin $II_B$ according to claim 1 in combination with a synegistically effective amount of a known synergistin or a soluble synergistin of formula:



in which Y denotes a hydrogen atom or a dimethylamino radical and

(1) either denotes a single bond, Z and $R_1$ denote a hydrogen atom and X denotes a radical of formula:



in which:

either $R_2$ denotes a hydrogen atom and $R_3$ denotes a hydroxy or alkyl radical unsubstituted or substituted by a carboxy, alkyloxycarbonyl, hydroxy, alkylamino or dialkylamino radical whose alkyl radicals can form, with the nitrogen atom to which they are attached, a 4 to 7-member heterocyclic ring chosen from azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, N-alkylpiperazinyl and azepinyl, or $R_3$ denotes a cycloalkyl radical containing 3 to 7 carbon atoms or a saturated 4 to 7-membered heterocyclic ring chosen from the azetidine, pyrrolidine, piperidine and azepine rings, these heterocyclic rings being unsubstituted or substituted by an alkyl radical on the nitrogen atom,

$R_2$ denotes a formyl or alkylcarbonyl radical and $R_3$ denotes an alkyl radical substituted by a carboxy, alkylamino or dialkylamino radical whose alkyl radicals can form, with the nitrogen atom to which they are attached, a 4 to 7-membered heterocyclic ring chosen from azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, N-alkylpiperazinyl and azepinyl, or $R_3$ denotes a 4 to 7-membered heterocyclic ring chosen from azetidine, pyrrolidine, piperidine and azepine, these heterocyclic rings being unsubstituted or substituted by an alkyl radical on the nitrogen atom,

or $R_2$ and $R_3$, which are identical or different, each denote an alkyl radical which is unsubstituted or substituted by carboxy, alkyloxycarbonyl, hydroxy, alkylamino or dialkylamino whose alkyl radicals optionally form, with the nitrogen atom to which they are attached, a 4 to 7-membered heterocyclic ring chosen from azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, N-alkylpiperazinyl and azepinyl-or $R_2$ and $R_3$ form, together with the nitrogen atom to which they are attached, a 4 to 7-membered heterocyclic ring chosen from the azetidine, pyrrolidine, piperidine, morpholine and

piperazine rings, optionally substituted by an alkyl radical,

(2) or ==== denotes a double bond, X denotes an oxygen atom and Z denotes a radical of formula:

in which:

(a) either $R_1$ and $R_5$ each denote a hydrogen atom and $R_4$ denotes a 3-pyrrolidinylthio or 3- or 4-piperidylthio radical (these radicals being optionally substituted by an alkyl radical) or $R_4$ denotes an alkylthio radical substituted by one or two hydroxysulphonyl, alkylamino or dialkylamino (optionally substituted by a mercapto or dialkylamino radical) radicals or by one or two rings chosen from piperazino (optionally substituted by an alkyl or mercaptoalkyl radical), morpholino, thiomorpholino, piperidino, 1-pyrrolidinyl, 2, 3 or 4-piperidyl and 2- or 3-pyrrolidinyl (these last two rings being optionally substituted by an alkyl radical on the nitrogen atom),

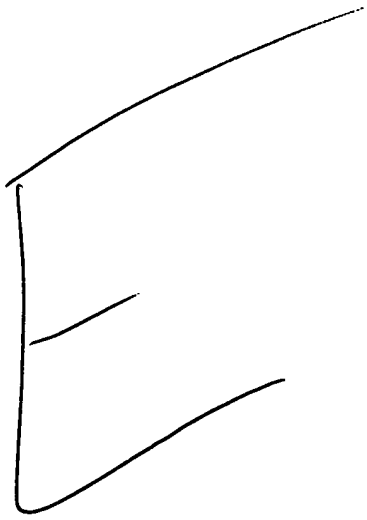
(b) or $R_1$ and $R_5$ together form a valency bond and $R_4$ denotes a 3-pyrrolidinylamino, 3- or 4-piperidylamino, 3-pyrrolidinyloxy, 3- or 4-piperidyloxy, 3-pyrrolidinylthio, 3- or 4-piperidylthio radical (these radicals being optionally substituted by an alkyl radical on the nitrogen atom in the ring), or $R_4$ denotes an alkylamino, alkyloxy or alkylthio radical substituted by one or two hydroxy-sulphonyl, alkylamino, dialkylamino (optionally substituted by a dialkylamino radical), trialkylammonio or 4- or 5-imidazolyl radicals, or by one or two rings chosen from piperazino (optionally substituted by an alkyl or mercaptoalkyl radical), morpholino, thiomorpholino, piperidino, 1-pyrrolidinyl, 2, 3 or 4-piperidyl and 2- or 3-pyrrolidinyl (these two latter rings being optionally substituted by an alkyl radical on the nitrogen atom), it being understood that the alkyl radicals and alkyl moieties referred to in the symbols defined above contain 1 to 5 carbon atoms and form a linear or branched chain, if appropriate in the form of one of its isomers or their mixtures, and optionally in the form of an acid addition salt, a metal salt or an addition salt with a nitrogen-containing organic base.

8. A pharmaceutical composition according to claim 7 which also contains a compatible pharmaceutically acceptable carrier and/or adjuvant.

9. A pharmaceutical composition comprising an effective amount of a pristinamycin $II_B$ according to claim 1 in association with a compatible pharmaceutically acceptable carrier and/or adjuvant.

10. Method of controlling bacterial growth which comprises exposing said bacteria to the effect of a pristinamycin $II_B$ according to claim 1 in sufficient concentration to control said bacteria.

* * * * *



TLI | CEV

PLEASE STAMP TO ACKNOWLEDGE RECEIPT OF THE FOLLOWING:

In re U.S. Patent No. 4,668,669
Inventors: Jean-Claude Barriere et al.
Issued: May 26, 1987
Title: PRISTINAMYCIN $II_B$ DERIVATIVES AND COMPOSITIONS CONTAINING THEM

**********

Enclosed:

1. Request for Certificate of Correction
2. PTO Form 1050 (10 pages - in duplicate)
3. Check in the amount of $100.00

**********


Date: 11/02/99 **HAND CARRY**
Case Ref.: 3804.0055 **CERTIFICATE OF CORRECTIONS BRANCH**
CEVanHorn/C. Woods (M.D. 701) **CRYSTAL PARK 3 - ROOM 918**
**ATTN: MINIKA BROWN**

PATENT
Attorney Docket No. 3804.0055-00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No.: 4,668,669 )
)
Inventors: Jean-Claude BARRIERE et al. )
)
Issue Date: May 26, 1987 )
)
For: PRISTINAMYCIN $II_B$ DERIVATIVES )
AND COMPOSITIONS CONTAINING )
THEM )

Certificate of Correction Branch

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

REQUEST FOR CERTIFICATE OF CORRECTION

Pursuant to 35 U.S.C. § 255 and 37 C.F.R. § 1.323, this is a request for the issuance of a Certificate of Correction in the above-identified patent. Two (2) copies of PTO Form 1050 are appended. The complete Certificate of Correction involves ten (10) pages.

The mistakes identified in the appended Form are of a clerical or typographical nature, or of minor character, and resulted from either an error of the Patent and Trademark Office or an error made in good faith by applicants. A certificate of correction is being filed to correct errors in various structured formulae and a typographical error or an error of minor character in the species recited in claim 5. No new matter is added because the compound as amended is explicitly supported in

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202-408-4000

Example 24 (col. 61) and no reexamination is required because the claimed compound is a species within allowed generic claim 1.

A check in the amount of $100 (the fee set forth in 37 C.F.R. § 1.20(a)) is appended to cover the costs of issuing this Certificate. Should a check not be appended or should any additional fees be needed, authorization is hereby given to charge any fees due in connection with the filing of this request to Deposit Account No. 06-0916.

Issuance of the Certificate of Correction containing the correction is earnestly requested.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

By: Charles E Van Horn
Charles E. Van Horn
Reg. No. 40,266

Dated: November 2, 1999

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UNITED STATES PATENT AND TRADEMARK OFFICE

# CERTIFICATE OF CORRECTION

PATENT NO.: 4,668,669

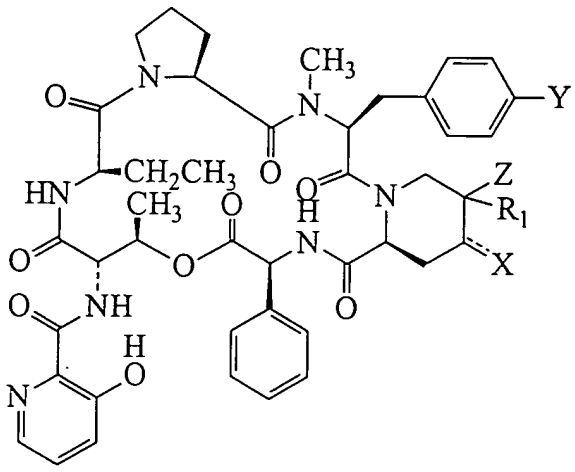


DATED: May 26, 1987

INVENTOR(S): Jean-Claude Barriere et al.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page, second column, delete the second formula and substitute:

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Garrett & Dunner, L.L.P.
1300 I Street, N.W.
Washington, DC 20005-3315

PATENT NO. 4,668,669

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UNITED STATES PATENT AND TRADEMARK OFFICE

# CERTIFICATE OF CORRECTION

PATENT NO.: 4,668,669



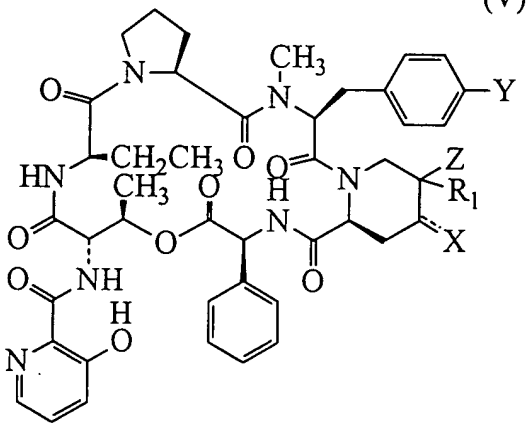
DATED: May 26, 1987

INVENTOR(S): Jean-Claude Barriere et al.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 13, lines 1-18, delete Formula (V) and substitute:

(V)



Mailing Address of Sender:

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1300 I Street, N.W.
Washington, DC 20005-3315

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UNITED STATES PATENT AND TRADEMARK OFFICE

# CERTIFICATE OF CORRECTION

PATENT NO.: 4,668,669



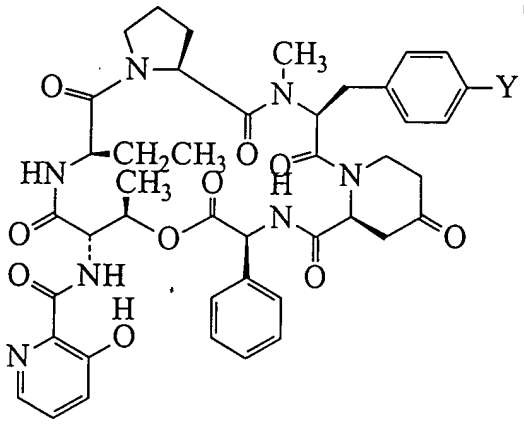
DATED: May 26, 1987

INVENTOR(S): Jean-Claude Barriere et al.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 15, lines 1-18, delete Formula (IX) and substitute:

(IX)



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UNITED STATES PATENT AND TRADEMARK OFFICE

# CERTIFICATE OF CORRECTION

PATENT NO.: 4,668,669



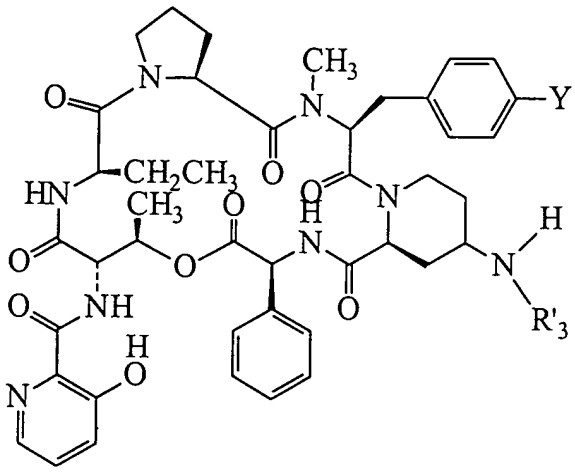
DATED: May 26, 1987

INVENTOR(S): Jean-Claude Barriere et al.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 16, lines 1-18, delete Formula (XI) and substitute:

(XI)



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UNITED STATES PATENT AND TRADEMARK OFFICE

# CERTIFICATE OF CORRECTION

PATENT NO.: 4,668,669



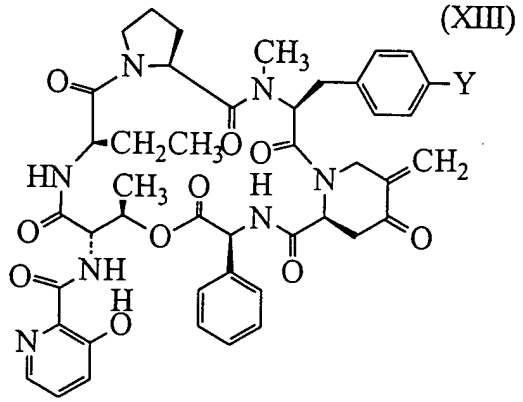
DATED: May 26, 1987

INVENTOR(S): Jean-Claude Barriere et al.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 17, lines 1-18, delete Formula (XIII) and substitute:

(XIII)



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UNITED STATES PATENT AND TRADEMARK OFFICE

# CERTIFICATE OF CORRECTION

PATENT NO.: 4,668,669



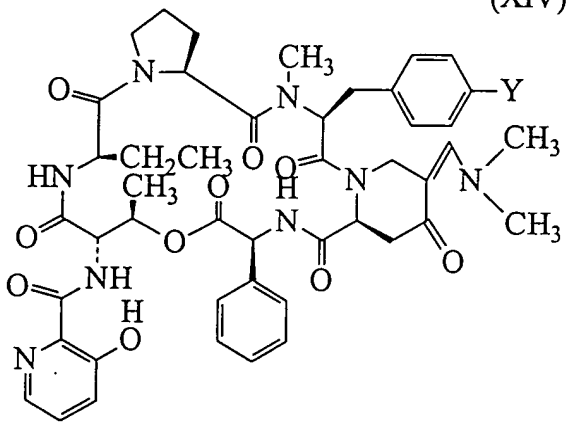
DATED: May 26, 1987

INVENTOR(S): Jean-Claude Barriere et al.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 17, lines 32-48, delete Formula (XIV) and substitute:

(XIV)



Mailing Address of Sender:

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UNITED STATES PATENT AND TRADEMARK OFFICE

# CERTIFICATE OF CORRECTION

PATENT NO.: 4,668,669



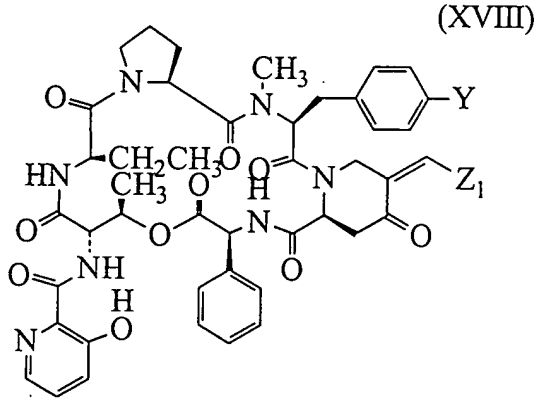
DATED: May 26, 1987

INVENTOR(S): Jean-Claude Barriere et al.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 18, lines 47-62, delete Formula (XVIII) and substitute:

(XVIII)



Mailing Address of Sender:

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# CERTIFICATE OF CORRECTION

PATENT NO.: 4,668,669



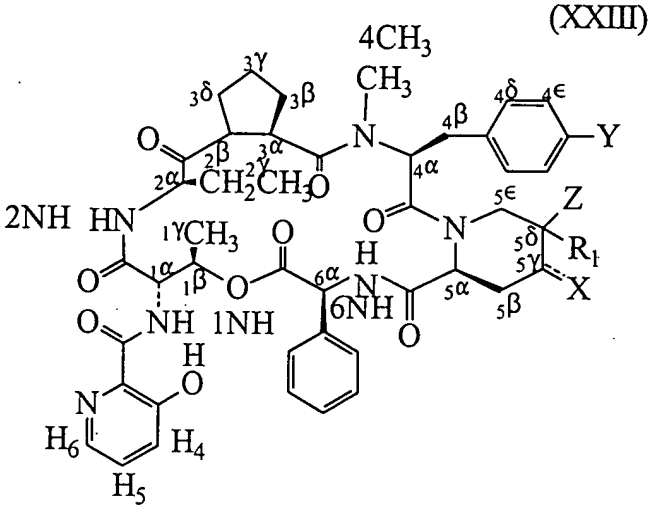
DATED: May 26, 1987

INVENTOR(S): Jean-Claude Barriere et al.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 23, lines 4-22, delete Formula (XXIII) and substitute:

(XXIII)



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# CERTIFICATE OF CORRECTION

PATENT NO.: 4,668,669



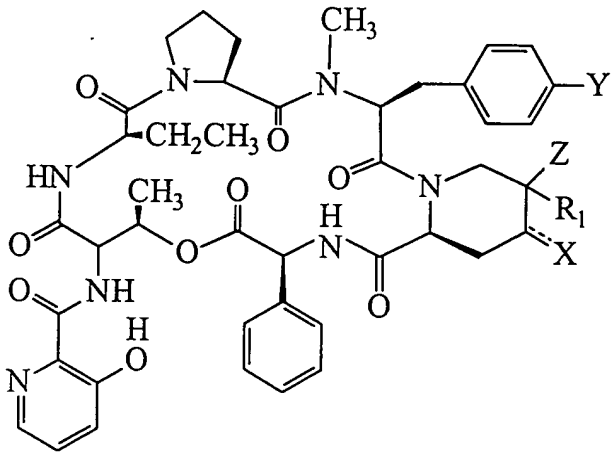
DATED: May 26, 1987

INVENTOR(S): Jean-Claude Barriere et al.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In claim 5, delete line 2 (col. 85, line 56) and substitute --26(2-diethylaminoethyl) sulphonylpristinamycin $II_B$ --

In claim 7 (col. 86, lines 1-17) delete the formula and substitute:



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UNITED STATES PATENT AND TRADEMARK OFFICE

# CERTIFICATE OF CORRECTION

PATENT NO.: 4,668,669 

DATED: May 26, 1987

INVENTOR(S): Jean-Claude Barriere et al.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Claim 7, line 22 (col. 86), after "either" insert -- --- --

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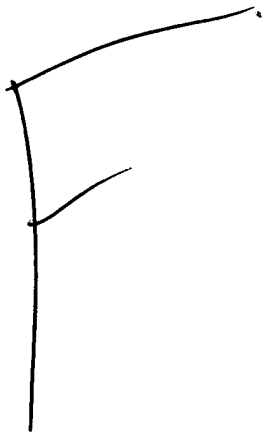

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Patent and Trademark Office
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M75W7

MARTIN F. SAVITZKY
RHONE-POULENC RORER INC.
500 ARCOLA ROAD
P.O. BOX 1200
COLLEGEVILLE PA 19426-0107

# MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 11, "STAT" below.

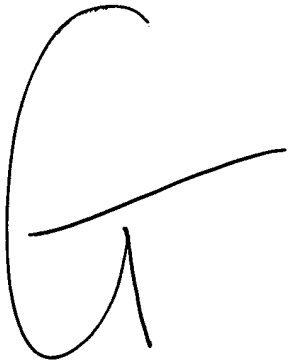
If a maintenance fee payment is defective, the reason is indicated by code in column 11, "STAT" below. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

| ITEM NBR | PATENT NUMBER | FEE CDE | FEE AMT | SUR CHARGE | SERIAL NUMBER | PATENT DATE | FILE DATE | PAY YR | SML ENT | STAT |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 4,668,669 | 185 | 3160 | ---- | 06/817,548 | 05/26/87 | 01/10/86 | 12 | NO | PAID |

| ITM NBR | ATTY DKT NUMBER |
|---|---|
| 1 | EHM 24059 |

**DIRECT THE RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO: COMMISIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, D.C. 20231**



**RP59500 Synercid®**

**IND 38,585 / NDA 50-748 and**
**IND 45,304/ NDA 50-747**

**Chronology of major events - KEY MEETINGS**

1994

| | |
|---|---|
| 04 May. 94 | Subpart E program meeting |
| 20 May 94 | Microbiology teleconference |
| 13 Jun 94 | End Phase II Meeting |

1995

| | |
|---|---|
| 17 April 95 | Teleconference on Scientific content & format of NDA |

1996

| | |
|---|---|
| 2 Apr 96 | CMC Technical Meeting |
| 30 Aug. 96 | Biopharmaceutics teleconference |
| 03 Sept. 96 | Microbiology videoconference |
| 05 Sept. 96 | Clinical Issues teleconference |
| 06 Nov. 96 | Pre-NDA meeting |

1997

| | |
|---|---|
| 15 Jan. 97 | CANDA demonstration |
| 30 May 97 | Discussion on emergence of VRSA in Japan |
| 14 Nov. 97 | Discuss telephone Informed Consent in emergency situations. |

1998

| | |
|---|---|
| 23 Jan 98 | Teleconference to discuss clinical and microbiology issues |
| 28 Jan 98 | Videoconference to discuss/prepare for FDA Advisory Committee Mtg. |
| 12 Feb 98 | Meeting to discuss/prepare for FDA Advisory Committee Mtg. |

**RP59500 Synercid®**

**IND 38,585 / NDA 50-748 and**
**IND 45,304/ NDA 50-747**

**Chronology of major events - KEY MEETINGS**

| | |
|---|---|
| 19 Feb. 98 | FDA Advisory Committee meeting. |
| 6 Mar 98 | Teleconference: Questions about approvable letter for NDA 50-747 and draft VREF labeling |
| 11 May 98 | Phone Conference: Final agreement on vial and tray labeling |
| 7 Aug 98 | Phone Conference: IND on Clinical hold per GMP deficiencies at secondary manufacturing site |
| 14 Aug 98 | Phone conference: Synercid Emergency Use Program and supply allocation |
| 1 Oct 98 | Teleconference: Questions about approvable letter for NDA 50-748 and labeling |

1999

| | |
|---|---|
| 3 Feb 99 | Teleconference: Agree to submission specifics for alternate manufacturing site (Catalytica) |
| 25 Feb 99 | Teleconference: VREF Confirmatory Protocol #396 design discussion |
| 28 Apr 99 | Teleconference: VREF Confirmatory Protocol #396 design discussion |
| 12 May 99 | Final Label Review Meeting |
| 24 May 99 | Phone Conference: FDA Release of IND Clinical Hold |
| 7 Jun 99 | Teleconference: FDA agrees that labeling is final |
| 22 Jul 99 | Teleconference: FDA agrees to final pediatric development strategy |

**RP59500 Synercid®**

**IND 38,585 / NDA 50-748 and**
**IND 45,304 / NDA 50-747**

**KEY SUBMISSIONS / FDA REQUESTS**

1991

| | |
|---|---|
| 31 Dec. 91 | IND #38585 original submission |

1993

| | |
|---|---|
| 30 Mar. 93 | Annual Report (30 Jan. 92 to 29 Jan. 93) |

1994

| | |
|---|---|
| 03 Mar. 94 | Response to 02 Feb. 94 request for additional information |
| 30 Mar. 94 | Request for end of Phase II meeting |
| 04 April 94 | Annual Report (30 Jan. 93 to 29 Jan. 94) |
| 24 May 94 | IND 45,304 original submission |
| 02 June 94 | Providing preliminary phase III information |
| 29 Aug. 94 | Clarification of question requesting a response during the end of phase II meeting |
| 22 Sep. 94 | Providing desk copies of clinical info. requested on 26 Aug. 94 |
| 14 Nov. 94 | Response to CMC questions/comments faxed to RPR on 25 Jul. 94. |
| 30 Nov. 94 | FDA fax containing 4 pages of chemistry comments. |

1995

| | |
|---|---|
| 05 April 95 | Annual Report (30 Jan. 94 to 29 Jan. 95) |
| 16 May 95 | Amendment/CMC : 15 chemistry comments |
| 22 May 95 | Authorization to export to Japan (request from RPR dated 13 mar. 95) |
| 05 Sept. 95 | Request for pre-NDA meeting. |

**RP59500 Synercid®**

**IND 38,585 / NDA 50-748 and**
**IND 45,304 / NDA 50-747**

**KEY SUBMISSIONS / FDA REQUESTS**

| | |
|---|---|
| 30 Oct. 95 | Change of manufacturing site for drug substance |

1996

| | |
|---|---|
| 13 March 96 | Pre meeting CMC briefing document |
| 29 March 96 | Annual Report (30 Jan. 95 to 29 Jan. 96) |
| 05 April 96 | Briefing Documents for 17 April teleconference (after this submission teleconference was cancelled) |
| 02 May 96 | RPR requests authorization to export to France for use in Emergency compassionate clinical trials. |
| 11 June 96 | FDA requests a list of preclinical pharmacokinetic / toxicokinetic data that will be included in NDA. |
| 02 July 96 | Response to FDA request for information (CANDA + CRF's). |
| 22 Oct. 96 | Briefing document for pre-NDA meeting |
| 14 Nov. 96 | Phone contact to inform FDA of NDA delay |

1997

| | |
|---|---|
| 02 April 97 | Annual Report (30 Jan. 96 to 29 Jan. 97) |
| 05 Sept. 97 | NDA 50747 and 50748 submitted to FDA |
| 08 Sept. 97 | Sent to FDA :<br>• copy of the draft antimicrobial monograph,<br>• CD containing the overall summary (item 2) of the NDA.<br>• yield copy of the CMC section of NDA. |
| 01 Oct. 97 | Information regarding Investigator lists sent to FDA. |
| 07 Oct. 97 | Table formats to summarize reasons for non-evaluability sent to FDA. |
| 05 Nov. 97 | Response to FDA request for information about skin studies. |

**RP59500 Synercid®**

**IND 38,585 / NDA 50-748 and**
**IND 45,304 / NDA 50-747**

**KEY SUBMISSIONS / FDA REQUESTS**

| | |
|---|---|
| 04 Dec. 97 | To FDA : 2 tables each providing list of patients with polymicrobic infections and list of reasons why CAP patients withdrew from study. |
| 18 Dec. 97 | Response to FDA request for information about microbiology. |

1998

| | |
|---|---|
| 09 Jan. 98 | To FDA :<br>• copy of the report of the vial-container closure test results.<br>• immersion test for the integrity of container closure system used for vials.<br>• response to 31 Dec. 97 microbiology questions<br>• response to 23 Dec. 97 microbiology questions |
| 22 Jan. 98 | Briefing document for FDA Advisory Committee Meeting. |
| 2 Mar 98 | CMC Submission RE: Lyophilizer, etc. |
| 05 March 98 | Approvable letter received for NDA 50-747. |
| 09 March 98 | Request for action preceding resolution of manufacturing issues |
| 27 March 98 | Provided list of ongoing studies, number of patients enrolled to date and approximate enrollment rate per month. |
| 09 Apr 98 | Provided listings for patients with total bilirubins and the liver safety board meeting minutes requested in 19 May fax |
| 20 Apr 98 | Annual Report (30 Jan 97 to 29 Jan 98) |
| 06 Jul 98 | Additional Microbiology analyses submitted |
| 21 Jul 98 | FDA request for Synercid Safety Data |
| 7 Aug 98 | FDA IND Clinical Hold Letter |

**RP59500 Synercid®**

**IND 38,585 / NDA 50-748 and**
**IND 45,304 / NDA 50-747**

**KEY SUBMISSIONS / FDA REQUESTS**

| | |
|---|---|
| 7 Aug 98 | FDA IND Clinical Hold Letter |
| 10 Aug 98 | IND Clinical Hold Response |
| 14 Aug 98 | Distribution of Synercid for Emergency Use during Clinical Hold |
| 4 Sep 98 | Approvable letter received for NDA 50-748 |
| 2 Oct 98 | Updated Investigators Brochure |
| 04 Nov 98 | FDA Fax with questions RE: VREF Confirmatory Study #396 |
| 23 Nov 98 | Updated Version of VREF Confirmatory Protocol #396 |
| 23 Nov 98 | Final Study Report of Population PK Study |
| 16 Dec 98 | Response to Issues Raised in NDA 50-748 approvable letter plus Additional Safety data requested 21 Jul 98 |

1999

| | |
|---|---|
| 15 Jan 99 | Response to Issues Raised in 50-747 approvable letter |
| 02 Feb 99 | RPR Fax documenting questions related to Catalytica Manufacturing site |
| 04 Mar 99 | Final Report Study #132 |
| 04 Mar 99 | Final Report Study #152 |
| 24 Mar 99 | Annual Report (30 Jan 98 to 29 Jan 99) |
| 13 Apr 99 | Final Labeling received from FDA by Fax |
| 10 May 99 | RPR fax with proposed labeling changes |
| 24 May 99 | Letter acknowledging lift of clinical hold |
| 18 Jun 99 | Promotional Materials for review - Wave 1 |

**RP59500 Synercid®**

**IND 38,585 / NDA 50-748 and**
**IND 45,304 / NDA 50-747**

**KEY SUBMISSIONS / FDA REQUESTS**

| | |
|---|---|
| 26 Aug 99 | Promotional Materials for review - Wave 2 |
| 30 Aug 99 | Written proposal regarding discontinuation of Emergency Use Program and use of Centeon-manufactured supplies |
| 9 Sep 99 | Promotional Materials for review - Wave 3 |
| 10 Sep 99 | Promotional Materials for review - Wave 4 |
| 14 Sep 99 | Promotional Materials for review - Wave 5 |
| 21 Sep 99 | Approval letter for NDA 50-747 and 50-748 |
| 21 Sep 99 | Fax copy of RPR press release |

Rhône-Poulenc Rorer Central Research

Regulatory Affairs

# APPLICATION CHRONOLOGY REPORT

## Report Cover Page

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Selection Criteria

App Number : 50747

Type : NDA

Drug Code: RP 59500

Trade Name: SYNERCID

Route of Administration : I.V. Dosage Form : INFUSION

Generic Name: pristinamycin 500mg / vial.

Ending Date: 21-sep-1999

| COMM DATE | COMM TYPE | DESCRIPTION | |
|---|---|---|---|
| 05-SEP-1997 | ORIGINAL SUBMISSION | CMC | DRUG SUBSTANCE |
| | ORIGINAL SUBMISSION | CMC | DRUG PRODUCT |
| | ORIGINAL SUBMISSION | LABEL | |
| | ORIGINAL SUBMISSION | 43 CLINICAL | SUMMARIES |
| | ORIGINAL SUBMISSION | CLINICAL | CRF |
| | ORIGINAL SUBMISSION | PRECLINICAL | PHARMACOLOGY |
| | ORIGINAL SUBMISSION | PRECLINICAL | DRUG SAFETY |
| | ORIGINAL SUBMISSION | PRECLINICAL | DRUG DISPO |
| | ORIGINAL SUBMISSION | PHARMACOKINETICS | |
| | ORIGINAL SUBMISSION | MICROBIOLOGY | |
| 15-SEP-1997 | GENERAL CORRESP From FDA | OTHER | |
| 19-SEP-1997 | GENERAL CORRESP To FDA | CLINICAL | STUDY |
| 27-OCT-1997 | GENERAL CORRESP To FDA | CLINICAL | STUDY |
| 07-NOV-1997 | GENERAL CORRESP To FDA | CLINICAL | STUDY |
| 12-NOV-1997 | PHONE CALL | CMC | DRUG SUBSTANCE |
| 22-DEC-1997 | PHONE CALL | MICROBIOLOGY | |
| 23-DEC-1997 | PHONE CALL | CLINICAL | STUDY |
| 05-JAN-1998 | AMENDMENT | SAFETY UPDATE | |
| 18-FEB-1998 | GENERAL CORRESP To FDA | CMC | DRUG PRODUCT |
| 04-MAR-1998 | GENERAL CORRESP To FDA | CLINICAL | STUDY |
| 05-MAR-1998 | GENERAL CORRESP From FDA | CMC | DRUG SUBSTANCE |
| | GENERAL CORRESP From FDA | CMC | DRUG PRODUCT |
| | GENERAL CORRESP From FDA | LABEL | |
| | GENERAL CORRESP From FDA | CLINICAL | STUDY |
| | GENERAL CORRESP From FDA | OTHER | APPROVABLE LETTER |

| COMM DATE | COMM TYPE | DESCRIPTION | |
|---|---|---|---|
| 05-MAR-1998 | GENERAL CORRESP From FDA | OTHER | FAX FROM FDA |
| 05-MAR-1998 | GENERAL CORRESP From FDA | OTHER | COPY OF MINUTES FROM TELECONFERENCE |
| 11-MAR-1998 | GENERAL CORRESP To FDA | OTHER | INTENTION TO AMEND APPLICATION |
| 19-MAR-1998 | GENERAL CORRESP From FDA | OTHER | COPY OF MINUTES |
| 03-APR-1998 | GENERAL CORRESP To FDA | LABEL | |
| 14-APR-1998 | GENERAL CORRESP To FDA | CLINICAL | STUDY |
| 14-APR-1998 | GENERAL CORRESP To FDA | CLINICAL | STUDY |
| 15-APR-1998 | GENERAL CORRESP From FDA | OTHER | COPY OF MINUTES |
| 24-APR-1998 | GENERAL CORRESP To FDA | LABEL | |
| 05-MAY-1998 | GENERAL CORRESP To FDA | CMC | DRUG SUBSTANCE |
| 05-MAY-1998 | GENERAL CORRESP To FDA | LABEL | |
| 05-MAY-1998 | GENERAL CORRESP To FDA | LABEL | |
| 28-MAY-1998 | GENERAL CORRESP From FDA | CLINICAL | STUDY |
| 02-JUN-1998 | MEETING MINUTES | OTHER | MEETING MINUTES |
| 08-JUN-1998 | GENERAL CORRESP To FDA | LABEL | |
| 08-JUN-1998 | PHONE CALL | LABEL | |
| 09-JUN-1998 | GENERAL CORRESP To FDA | CLINICAL | STUDY |
| 09-JUN-1998 | PHONE CALL | CLINICAL | STUDY |
| | PHONE CALL | CMC | DRUG SUBSTANCE |
| 30-JUN-1998 | MEETING MINUTES | OTHER | FDA TELECONFERENCE MEETING MINUTES |
| 14-JUL-1998 | GENERAL CORRESP To FDA | LABEL | PACKAGE INSERT |
| 14-JUL-1998 | PHONE CALL | LABEL | |
| | PHONE CALL | CMC | DRUG SUBSTANCE |
| 14-JUL-1998 | PHONE CALL | CLINICAL | STUDY |
| 15-JUL-1998 | PHONE CALL | CMC | DRUG SUBSTANCE |
| 16-JUL-1998 | PHONE CALL | CLINICAL | STUDY |

| COMM DATE | COMM TYPE | DESCRIPTION | |
|---|---|---|---|
| 21-JUL-1998 | PHONE CALL | CLINICAL | STUDY |
| 21-JUL-1998 | PHONE CALL | CLINICAL | STUDY |
| 23-JUL-1998 | GENERAL CORRESP To FDA | CLINICAL | STUDY |
| 23-JUL-1998 | PHONE CALL | LABEL | |
| 24-JUL-1998 | PHONE CALL | CLINICAL | STUDY |
| 27-JUL-1998 | PHONE CALL | CLINICAL | STUDY |
| 28-JUL-1998 | GENERAL CORRESP From FDA | CLINICAL | STUDY |
| 28-JUL-1998 | PHONE CALL | CLINICAL | STUDY |
| 31-JUL-1998 | GENERAL CORRESP To FDA | CMC | DRUG SUBSTANCE |
| 12-AUG-1998 | GENERAL CORRESP To FDA | LABEL | |
| 12-AUG-1998 | PHONE CALL | OTHER | DISCUSSION |
| 13-AUG-1998 | PHONE CALL | OTHER | |
| 14-AUG-1998 | PHONE CALL | CLINICAL | STUDY |
| 19-AUG-1998 | PHONE CALL | CMC | DRUG SUBSTANCE |
| 26-AUG-1998 | PHONE CALL | CLINICAL | STUDY |
| 26-AUG-1998 | PHONE CALL | CMC | DRUG SUBSTANCE |
| 31-AUG-1998 | PHONE CALL | CLINICAL | STUDY |
| 14-SEP-1998 | PHONE CALL | CLINICAL | STUDY |
| 14-SEP-1998 | PHONE CALL | OTHER | ANTI-INFECTIVE ADVISORY MEETING |
| 16-SEP-1998 | GENERAL CORRESP To FDA | CLINICAL | CRF |
| 16-SEP-1998 | PHONE CALL | OTHER | ANTI-INFECTIVE ADVISORY MEETING |
| 21-SEP-1998 | PHONE CALL | OTHER | ANTI-INFECTIVE ADVISORY MEETING |
| 24-SEP-1998 | PHONE CALL | LABEL | PACKAGE INSERT |
| 08-OCT-1998 | PHONE CALL | CLINICAL | STUDY |
| 19-OCT-1998 | GENERAL CORRESP To FDA | LABEL | |
| 20-OCT-1998 | PHONE CALL | OTHER | MEETING MINUTES |

| COMM DATE | COMM TYPE | DESCRIPTION | |
|---|---|---|---|
| 22-OCT-1998 | GENERAL CORRESP To FDA | OTHER | REQUEST FOR COMMENTS |
| 27-OCT-1998 | PHONE CALL | CLINICAL | STUDY |
| 29-OCT-1998 | PHONE CALL | OTHER | CONFIRM AGREEMENT |
| 04-NOV-1998 | GENERAL CORRESP From FDA | CLINICAL | STUDY |
| 23-NOV-1998 | GENERAL CORRESP | CLINICAL | STUDY |
| 02-DEC-1998 | GENERAL CORRESP | CLINICAL | STUDY |
| 02-DEC-1998 | PHONE CALL | CLINICAL | STUDY |
| 08-DEC-1998 | PHONE CALL | CLINICAL | STUDY |
| 10-DEC-1998 | PHONE CALL | OTHER | PROPOSAL |
| 11-DEC-1998 | GENERAL CORRESP To FDA | CLINICAL | STUDY |
| 14-DEC-1998 | PHONE CALL | CMC | DRUG PRODUCT |
| | PHONE CALL | CLINICAL | STUDY |
| 17-DEC-1998 | GENERAL CORRESP To FDA | LABEL | |
| 17-DEC-1998 | GENERAL CORRESP To FDA | LABEL | |
| 18-DEC-1998 | GENERAL CORRESP To FDA | CMC | DRUG SUBSTANCE |
| 29-DEC-1998 | PHONE CALL | CMC | DRUG PRODUCT |
| 29-DEC-1998 | PHONE CALL | CLINICAL | SAFETY REPORT |
| 05-JAN-1999 | PHONE CALL | LABEL | |
| 05-JAN-1999 | PHONE CALL | CLINICAL | SAFETY REPORT |
| 13-JAN-1999 | PHONE CALL | CLINICAL | STUDY |
| 15-JAN-1999 | GENERAL CORRESP To FDA | CLINICAL | STUDY |
| 19-JAN-1999 | PHONE CALL | OTHER | DISCUSS MISC ISSUES |
| 21-JAN-1999 | PHONE CALL | OTHER | DISCUSS MISC ISSUES |
| 25-JAN-1999 | GENERAL CORRESP To FDA | CLINICAL | STUDY |
| 25-JAN-1999 | PHONE CALL | LABEL | |
| | PHONE CALL | OTHER | LABEL REVIEW MEETING |

| COMM DATE | COMM TYPE | DESCRIPTION | |
|---|---|---|---|
| 26-JAN-1999 | GENERAL CORRESP To FDA | OTHER | SUMMARY OF PLANS |
| 26-JAN-1999 | PHONE CALL | OTHER | QUESTION |
| 29-JAN-1999 | GENERAL CORRESP To FDA | CLINICAL | CRF |
| 01-FEB-1999 | PHONE CALL | OTHER | FOLLOW-UP |
| 02-FEB-1999 | GENERAL CORRESP To FDA | CMC | DRUG PRODUCT |
| 02-FEB-1999 | PHONE CALL | CMC | DRUG PRODUCT |
| 09-FEB-1999 | PHONE CALL | LABEL | |
| 18-FEB-1999 | PHONE CALL | LABEL | |
| 22-FEB-1999 | MEETING MINUTES | CLINICAL | STUDY |
| | MEETING MINUTES | CMC | DRUG PRODUCT |
| 23-FEB-1999 | GENERAL CORRESP To FDA | OTHER | |
| 23-FEB-1999 | PHONE CALL | CLINICAL | STUDY |
| | PHONE CALL | LABEL | |
| | PHONE CALL | OTHER | TELECONFERENCE |
| 25-FEB-1999 | PHONE CALL | CLINICAL | STUDY |
| 01-MAR-1999 | GENERAL CORRESP To FDA | OTHER | |
| 04-MAR-1999 | GENERAL CORRESP To FDA | CLINICAL | STUDY |
| 09-MAR-1999 | PHONE CALL | CMC | DRUG PRODUCT |
| 10-MAR-1999 | MEETING MINUTES | CLINICAL | STUDY |
| 15-MAR-1999 | GENERAL CORRESP To FDA | CLINICAL | STUDY |
| 17-MAR-1999 | PHONE CALL | LABEL | |
| 23-MAR-1999 | GENERAL CORRESP To FDA | CLINICAL | STUDY |
| 23-MAR-1999 | PHONE CALL | LABEL | |
| 26-MAR-1999 | GENERAL CORRESP To FDA | CMC | DRUG PRODUCT |
| 29-MAR-1999 | PHONE CALL | LABEL | |
| 07-APR-1999 | PHONE CALL | LABEL | |

| COMM DATE | COMM TYPE | DESCRIPTION | |
|---|---|---|---|
| 08-APR-1999 | MEETING MINUTES | CLINICAL | STUDY |
| 13-APR-1999 | GENERAL CORRESP From FDA | LABEL | |
| 13-APR-1999 | PHONE CALL | LABEL | |
| 13-APR-1999 | PHONE CALL | LABEL | |
| 27-APR-1999 | GENERAL CORRESP To FDA | LABEL | |
| 27-APR-1999 | GENERAL CORRESP To FDA | LABEL | |
| 28-APR-1999 | PHONE CALL | CLINICAL | STUDY |
| 03-MAY-1999 | PHONE CALL | LABEL | |
| 10-MAY-1999 | GENERAL CORRESP To FDA | LABEL | PACKAGE INSERT |
| 10-MAY-1999 | PHONE CALL | LABEL | |
| 12-MAY-1999 | GENERAL CORRESP To FDA | OTHER | MINUTES OF FDA MEETING |
| 13-MAY-1999 | PHONE CALL | CLINICAL | STUDY |
| 18-MAY-1999 | GENERAL CORRESP From FDA | LABEL | |
| 20-MAY-1999 | GENERAL CORRESP To FDA | LABEL | |
| 20-MAY-1999 | PHONE CALL | OTHER | NUMEROUS ISSUES |
| 25-MAY-1999 | GENERAL CORRESP To FDA | CMC | DRUG PRODUCT |
| 25-MAY-1999 | GENERAL CORRESP To FDA | CMC | DRUG PRODUCT |
| 26-MAY-1999 | GENERAL CORRESP To FDA | CLINICAL | PROTOCOL AMENDMENT |
| 26-MAY-1999 | GENERAL CORRESP To FDA | CLINICAL | STUDY |
| 26-MAY-1999 | PHONE CALL | OTHER | NUMEROUS ISSUES |
| 02-JUN-1999 | PHONE CALL | LABEL | |
| 04-JUN-1999 | AMENDMENT | CMC | DRUG SUBSTANCE |
| 04-JUN-1999 | GENERAL CORRESP To FDA | CMC | DRUG PRODUCT |
| 07-JUN-1999 | MEETING MINUTES | CLINICAL | STUDY |
| 07-JUN-1999 | PHONE CALL | OTHER | NUMEROUS ISSUES |
| 10-JUN-1999 | PHONE CALL | OTHER | NUMEROUS ISSUES |

| COMM DATE | COMM TYPE | DESCRIPTION | |
|---|---|---|---|
| 17-JUN-1999 | PHONE CALL | CLINICAL | STUDY |
| 18-JUN-1999 | GENERAL CORRESP To FDA | LABEL | |
| 21-JUN-1999 | GENERAL CORRESP To FDA | CLINICAL | STUDY |
| 24-JUN-1999 | MEETING MINUTES | CLINICAL | STUDY |
| 24-JUN-1999 | PHONE CALL | OTHER | NUMEROUS ISSUES |
| 01-JUL-1999 | GENERAL CORRESP To FDA | CLINICAL | STUDY |
| 01-JUL-1999 | PHONE CALL | OTHER | NUMEROUS ISSUES |
| 06-JUL-1999 | MEETING MINUTES | LABEL | |
| 07-JUL-1999 | PHONE CALL | OTHER | NUMEROUS ISSUES |
| 08-JUL-1999 | GENERAL CORRESP To FDA | CLINICAL | STUDY |
| 08-JUL-1999 | GENERAL CORRESP To FDA | CLINICAL | PROTOCOL AMENDMENT |
| 08-JUL-1999 | PHONE CALL | LABEL | PACKAGE INSERT |
| 15-JUL-1999 | PHONE CALL | OTHER | NUMEROUS ISSUES |
| 21-JUL-1999 | GENERAL CORRESP From FDA | LABEL | COPY OF RESPONSE |
| 21-JUL-1999 | GENERAL CORRESP To FDA | CLINICAL | STUDY |
| | GENERAL CORRESP To FDA | CLINICAL | STUDY |
| 21-JUL-1999 | GENERAL CORRESP From FDA | LABEL | |
| 22-JUL-1999 | PHONE CALL | CMC | DRUG PRODUCT |
| 22-JUL-1999 | PHONE CALL | OTHER | REQUEST |
| 23-JUL-1999 | AMENDMENT | CMC | DRUG PRODUCT |
| 26-JUL-1999 | GENERAL CORRESP To FDA | CLINICAL | STUDY |
| 26-JUL-1999 | GENERAL CORRESP To FDA | CMC | DRUG PRODUCT |
| 26-JUL-1999 | PHONE CALL | CMC | DRUG PRODUCT |
| 28-JUL-1999 | AMENDMENT | CMC | DRUG PRODUCT |
| 02-AUG-1999 | GENERAL CORRESP To FDA | OTHER | LETTER |
| 04-AUG-1999 | GENERAL CORRESP To FDA | OTHER | FAX COPY |

| COMM DATE | COMM TYPE | DESCRIPTION | |
|---|---|---|---|
| 04-AUG-1999 | GENERAL CORRESP To FDA | CMC | DRUG PRODUCT |
| 04-AUG-1999 | PHONE CALL | OTHER | |
| 06-AUG-1999 | GENERAL CORRESP To FDA | CLINICAL | STUDY |
| 06-AUG-1999 | GENERAL CORRESP To FDA | LABEL | |
| 09-AUG-1999 | GENERAL CORRESP From FDA | CLINICAL | STUDY |
| 09-AUG-1999 | PHONE CALL | OTHER | NUMEROUS ISSUES |
| 10-AUG-1999 | GENERAL CORRESP To FDA | LABEL | PACKAGE INSERT |
| 10-AUG-1999 | GENERAL CORRESP From FDA | CMC | DRUG PRODUCT |
| 16-AUG-1999 | PHONE CALL | OTHER | REQUEST FOR TELECON |
| 17-AUG-1999 | GENERAL CORRESP To FDA | LABEL | PACKAGE INSERT |
| 17-AUG-1999 | GENERAL CORRESP To FDA | CLINICAL | STUDY |
| 17-AUG-1999 | GENERAL CORRESP To FDA | LABEL | |
| 17-AUG-1999 | GENERAL CORRESP To FDA | LABEL | |
| 17-AUG-1999 | PHONE CALL | OTHER | REQUEST |
| 18-AUG-1999 | GENERAL CORRESP To FDA | CMC | DRUG PRODUCT |
| 19-AUG-1999 | PHONE CALL | OTHER | DISCUSSION |
| 26-AUG-1999 | GENERAL CORRESP To FDA | LABEL | |
| 26-AUG-1999 | GENERAL CORRESP To FDA | LABEL | |
| 30-AUG-1999 | GENERAL CORRESP To FDA | CMC | DRUG PRODUCT |
| 30-AUG-1999 | GENERAL CORRESP To FDA | CLINICAL | STUDY |
| 31-AUG-1999 | PHONE CALL | CMC | DRUG PRODUCT |
| 02-SEP-1999 | GENERAL CORRESP To FDA | CLINICAL | STUDY |
| 02-SEP-1999 | GENERAL CORRESP To FDA | CLINICAL | STUDY |
| 02-SEP-1999 | GENERAL CORRESP From FDA | LABEL | |
| 02-SEP-1999 | GENERAL CORRESP From FDA | LABEL | |
| 02-SEP-1999 | PHONE CALL | CMC | DRUG PRODUCT |

| COMM DATE | COMM TYPE | DESCRIPTION | |
|---|---|---|---|
| 08-SEP-1999 | GENERAL CORRESP To FDA | LABEL | |
| 08-SEP-1999 | PHONE CALL | OTHER | INFORMATION |
| 09-SEP-1999 | GENERAL CORRESP To FDA | LABEL | |
| 10-SEP-1999 | GENERAL CORRESP To FDA | LABEL | |
| 10-SEP-1999 | GENERAL CORRESP To FDA | LABEL | |
| 10-SEP-1999 | GENERAL CORRESP To FDA | LABEL | |
| 14-SEP-1999 | GENERAL CORRESP To FDA | OTHER | DRAFT PRESS RELEASE |
| 14-SEP-1999 | GENERAL CORRESP To FDA | LABEL | |
| 14-SEP-1999 | GENERAL CORRESP To FDA | CLINICAL | STUDY |
| 14-SEP-1999 | GENERAL CORRESP To FDA | LABEL | |
| 14-SEP-1999 | PHONE CALL | OTHER | DISCUSSION |
| 15-SEP-1999 | PHONE CALL | LABEL | |
| 16-SEP-1999 | PHONE CALL | OTHER | DISCUSSION |
| 20-SEP-1999 | PHONE CALL | OTHER | NOTIFY REPORT |
| 21-SEP-1999 | GENERAL CORRESP From FDA | OTHER | APPROVAL LETTER FOR NDA 50-747 AND NDA 50-748 |
| 21-SEP-1999 | GENERAL CORRESP From FDA | LABEL | FDA COMMENTS ON DRAFT PRESS RELEASE |
| 21-SEP-1999 | GENERAL CORRESP From FDA | LABEL | RESPONSE |
| 21-SEP-1999 | GENERAL CORRESP From FDA | LABEL | OTHER RECOMMENDATIONS |
| 21-SEP-1999 | GENERAL CORRESP To FDA | LABEL | FAX COPY OF PRESS RELEASE |
| 21-SEP-1999 | GENERAL CORRESP From FDA | OTHER | FDA FAX COPY OF 21-SEP-99 APPROVAL ACTION LETTER |
| 21-SEP-1999 | PHONE CALL | LABEL | DISCUSSION |
| 21-SEP-1999 | PHONE CALL | OTHER | DISCUSSION |

Rhône-Poulenc Rorer Central Research

Regulatory Affairs

# APPLICATION CHRONOLOGY REPORT

Report Cover Page

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Selection Criteria

App Number : 45304

Type : IND

Drug Code : RP 59500

Trade Name: SYNERCID

Route of Administration : INJECTION Dosage Form : INFUSION

Generic Name : pristinamycin RP57669/54476 500mg.

Ending Date: 21-sep-1999

| COMM DATE | COMM TYPE | DESCRIPTION | |
|---|---|---|---|
| 24-MAY-1994 | ORIGINAL SUBMISSION | OTHER | INVESTIGATOR'S BROCHURE |
| | ORIGINAL SUBMISSION | CLINICAL | STUDY |
| 26-MAY-1994 | GENERAL CORRESP From FDA | OTHER | FDA ACKNOWLEGEMENT OF RECEIPT OF ORIG IND ON 24-MAY-94 |
| 06-JUN-1994 | AMENDMENT | CLINICAL | CRF |
| 07-JUN-1994 | AMENDMENT | OTHER | EXTRA COPIES |
| 07-JUN-1994 | AMENDMENT | CLINICAL | STUDY |
| 07-JUN-1994 | AMENDMENT | OTHER | REQUEST FOR TELEPHONE CONFERENCE |
| 11-JUL-1994 | PHONE CALL | CMC | DRUG PRODUCT |
| 12-JUL-1994 | AMENDMENT | CLINICAL | STUDY |
| 14-JUL-1994 | GENERAL CORRESP To FDA | CMC | DRUG PRODUCT |
| 25-JUL-1994 | AMENDMENT | CLINICAL | STUDY |
| 25-JUL-1994 | GENERAL CORRESP From FDA | CMC | DRUG SUBSTANCE |
| 25-JUL-1994 | PHONE CALL | CLINICAL | STUDY |
| 26-JUL-1994 | PHONE CALL | CLINICAL | STUDY |
| 27-JUL-1994 | AMENDMENT | CLINICAL | STUDY |
| 27-JUL-1994 | PHONE CALL | OTHER | CLARIFICATION OF SEVERAL POINTS |
| 29-JUL-1994 | GENERAL CORRESP To FDA | CLINICAL | CRF |
| 08-AUG-1994 | PHONE CALL | CLINICAL | STUDY |
| 16-AUG-1994 | PHONE CALL | CLINICAL | STUDY |
| 09-SEP-1994 | AMENDMENT | CLINICAL | SUMMARY |
| 19-SEP-1994 | PHONE CALL | OTHER | SCHEDULE PRE-NDA MEETING |
| 26-SEP-1994 | PHONE CALL | CMC | DRUG PRODUCT |
| 11-OCT-1994 | AMENDMENT | CLINICAL | STUDY |
| | AMENDMENT | CLINICAL | PROTOCOL AMENDMENT |
| 28-OCT-1994 | PHONE CALL | MICROBIOLOGY | VARIOUS ISSUES |
| 31-OCT-1994 | AMENDMENT | CLINICAL | STUDY |

| COMM DATE | COMM TYPE | DESCRIPTION | |
|---|---|---|---|
| 04-NOV-1994 | AMENDMENT | CLINICAL | STUDY |
| 04-NOV-1994 | AMENDMENT | CLINICAL | STUDY |
| 07-NOV-1994 | AMENDMENT | CLINICAL | STUDY |
| 07-NOV-1994 | PHONE CALL | MICROBIOLOGY | |
| 07-NOV-1994 | PHONE CALL | OTHER | VARIOUS ISSUES |
| 08-NOV-1994 | AMENDMENT | CLINICAL | STUDY |
| 10-NOV-1994 | AMENDMENT | CLINICAL | STUDY |
| 10-NOV-1994 | PHONE CALL | PHARMACOKINETICS | |
| 14-NOV-1994 | AMENDMENT | CLINICAL | STUDY |
| 14-NOV-1994 | AMENDMENT | CLINICAL | STUDY |
| 14-NOV-1994 | AMENDMENT | CMC | DRUG |
| 14-NOV-1994 | AMENDMENT | CMC | DRUG |
| 15-NOV-1994 | AMENDMENT | CLINICAL | STUDY |
| 23-NOV-1994 | PHONE CALL | OTHER | DISCUSS VARIOUS ISSUES |
| 06-DEC-1994 | AMENDMENT | CLINICAL | |
| 15-DEC-1994 | AMENDMENT | OTHER | MEETING REQUEST |
| 20-DEC-1994 | AMENDMENT | CMC | DRUG PRODUCT |
| 23-DEC-1994 | AMENDMENT | OTHER | ENCLOSED A LIST OF ISSUES |
| 23-DEC-1994 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 03-JAN-1995 | AMENDMENT | CLINICAL | STUDY |
| 05-JAN-1995 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 05-JAN-1995 | PHONE CALL | OTHER | PRE-NDA MEETING DISCUSSED |
| | PHONE CALL | PRECLINICAL | STUDY |
| | PHONE CALL | CLINICAL | STUDY |
| 12-JAN-1995 | MEETING MINUTES | OTHER | PRESENTED MEETING MINUTES |
| 12-JAN-1995 | MEETING MINUTES | OTHER | PROVIDED MEETING MINUTES |

| COMM DATE | COMM TYPE | DESCRIPTION | |
|---|---|---|---|
| 12-JAN-1995 | PHONE CALL | OTHER | FOLLOW-UP |
| 12-JAN-1995 | PHONE CALL | OTHER | PRE-NDA MEETING |
| 18-JAN-1995 | PHONE CALL | OTHER | DISCUSS SCHEDULING THE PRE-NDA MEETING |
| 30-JAN-1995 | AMENDMENT | CMC | DRUG PRODUCT |
| 31-JAN-1995 | PHONE CALL | OTHER | RECEIVE FEEDBACK RE: FDA'S INTERNAL MEETING |
| 03-FEB-1995 | PHONE CALL | OTHER | DISCUSS PROPOSAL |
| 07-FEB-1995 | AMENDMENT | CLINICAL | STUDY |
| 08-FEB-1995 | GENERAL CORRESP TO FDA | CLINICAL | STUDY |
| | GENERAL CORRESP TO FDA | CLINICAL | CRF |
| 08-FEB-1995 | GENERAL CORRESP From FDA | CMC | DRUG SUBSTANCE |
| 15-FEB-1995 | AMENDMENT | CLINICAL | PROTOCOL AMENDMENT |
| 21-FEB-1995 | PHONE CALL | OTHER | POSTPONE PRE-NDA MEETING |
| 06-MAR-1995 | AMENDMENT | CLINICAL | STUDY |
| 07-MAR-1995 | PHONE CALL | OTHER | PROTOCOL |
| 07-MAR-1995 | PHONE CALL | OTHER | |
| 10-MAR-1995 | AMENDMENT | CLINICAL | STUDY |
| 10-MAR-1995 | GENERAL CORRESP To FDA | CLINICAL | STUDY |
| 13-MAR-1995 | PHONE CALL | OTHER | APRIL 3 MEETING |
| 16-MAR-1995 | PHONE CALL | OTHER | APRIL 10TH MEETING |
| 16-MAR-1995 | PHONE CALL | CLINICAL | SAFETY |
| 17-MAR-1995 | FDA REPORT | CLINICAL | SAFETY |
| 17-MAR-1995 | GENERAL CORRESP From FDA | OTHER | FDA FAX TO CONFIRM MEETING |
| 22-MAR-1995 | PHONE CALL | OTHER | |
| 24-MAR-1995 | FDA REPORT | 5 CLINICAL | SAFETY REPORTS |
| 03-APR-1995 | AMENDMENT | OTHER | PROVIDED PRE-MEETING BRIEFING PACKAGE |
| 05-APR-1995 | FDA REPORT | ANNUAL RPT | |

| COMM DATE | COMM TYPE | DESCRIPTION | |
|---|---|---|---|
| 05-APR-1995 | PHONE CALL | OTHER | VREF MEETING |
| 05-APR-1995 | PHONE CALL | OTHER | PROTOCOL |
| 06-APR-1995 | AMENDMENT | CLINICAL | STUDY |
| 05-MAY-1995 | MEETING MINUTES | LABEL | |
| 11-MAY-1995 | AMENDMENT | CLINICAL | STUDY |
| 12-MAY-1995 | AMENDMENT | CLINICAL | STUDY |
| 16-MAY-1995 | AMENDMENT | CLINICAL | PROTOCOL AMENDMENT |
| 02-JUN-1995 | PHONE CALL | CLINICAL | SAFETY REPORT |
| 06-JUN-1995 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 27-JUN-1995 | AMENDMENT | CLINICAL | SAFETY REPORT |
| 10-JUL-1995 | AMENDMENT | CLINICAL | STUDY |
| 17-AUG-1995 | PHONE CALL | CLINICAL | SAFETY REPORT |
| 18-AUG-1995 | PHONE CALL | OTHER | |
| 22-AUG-1995 | AMENDMENT | CLINICAL | STUDY |
| 23-AUG-1995 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 05-SEP-1995 | AMENDMENT | CMC | DRUG SUBSTANCE |
| | AMENDMENT | CMC | DRUG PRODUCT |
| 12-SEP-1995 | PHONE CALL | CLINICAL | STUDY |
| 21-SEP-1995 | AMENDMENT | CLINICAL | STUDY |
| 21-SEP-1995 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 28-SEP-1995 | GENERAL CORRESP To FDA | CLINICAL | STUDY |
| 03-OCT-1995 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 04-OCT-1995 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 04-OCT-1995 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 06-OCT-1995 | AMENDMENT | OTHER | |
| 24-OCT-1995 | AMENDMENT | CLINICAL | STUDY |

| COMM DATE | COMM TYPE | DESCRIPTION | |
|---|---|---|---|
| 30-OCT-1995 | AMENDMENT | CMC | DRUG SUBSTANCE |
| 30-OCT-1995 | AMENDMENT | CLINICAL | STUDY |
| 09-NOV-1995 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 10-NOV-1995 | AMENDMENT | CLINICAL | STUDY |
| 17-NOV-1995 | PHONE CALL | OTHER | APPLICATION REVIEW |
| 06-DEC-1995 | AMENDMENT | CLINICAL | STUDY |
| 06-DEC-1995 | AMENDMENT | CLINICAL | STUDY |
| 08-DEC-1995 | PHONE CALL | CLINICAL | STUDY |
| 19-DEC-1995 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 21-DEC-1995 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 11-JAN-1996 | AMENDMENT | CLINICAL | STUDY |
| 15-JAN-1996 | AMENDMENT | CLINICAL | STUDY |
| 19-JAN-1996 | PHONE CALL | OTHER | |
| 29-JAN-1996 | AMENDMENT | CLINICAL | STUDY |
| 30-JAN-1996 | AMENDMENT | CLINICAL | STUDY |
| 06-FEB-1996 | PHONE CALL | OTHER | TECHNICAL MEETING |
| 07-FEB-1996 | PHONE CALL | OTHER | TECHNICAL MEETING |
| 13-FEB-1996 | PHONE CALL | OTHER | TECHNICAL MEETING |
| 14-FEB-1996 | PHONE CALL | OTHER | TECHNICAL MEETING |
| 15-FEB-1996 | PHONE CALL | OTHER | TECHNICAL MEETING |
| 23-FEB-1996 | PHONE CALL | CMC | DRUG PRODUCT |
| 23-FEB-1996 | PHONE CALL | CLINICAL | STUDY |
| 26-FEB-1996 | PHONE CALL | CLINICAL | STUDY |
| 27-FEB-1996 | GENERAL CORRESP To FDA | CLINICAL | STUDY |
| 27-FEB-1996 | PHONE CALL | CLINICAL | STUDY |
| 28-FEB-1996 | FDA REPORT | CLINICAL | SAFETY REPORT |

| COMM DATE | COMM TYPE | DESCRIPTION | |
|---|---|---|---|
| 28-FEB-1996 | PHONE CALL | CLINICAL | SAFETY REPORT |
| 01-MAR-1996 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 04-MAR-1996 | PHONE CALL | OTHER | TECHNICAL MEETING |
| 05-MAR-1996 | AMENDMENT | CLINICAL | STUDY |
| 05-MAR-1996 | AMENDMENT | CLINICAL | STUDY |
| 05-MAR-1996 | PHONE CALL | OTHER | TECHNICAL MEETING AVAILABILITY |
| 11-MAR-1996 | PHONE CALL | OTHER | CMC BRIEFING PACKAGE AND TECHNICAL MEETING SCHEDULING |
| 15-MAR-1996 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 19-MAR-1996 | PHONE CALL | OTHER | REVIEW |
| 20-MAR-1996 | PHONE CALL | OTHER | |
| 20-MAR-1996 | PHONE CALL | CMC | DRUG PRODUCT |
| 21-MAR-1996 | PHONE CALL | OTHER | REVIEW |
| 22-MAR-1996 | PHONE CALL | CMC | DRUG SUBSTANCE |
| 25-MAR-1996 | PHONE CALL | OTHER | CLINICAL MEETINGS |
| 25-MAR-1996 | PHONE CALL | CMC | DRUG SUBSTANCE |
| 27-MAR-1996 | GENERAL CORRESP From FDA | OTHER | FDA FAX CMC MEETING ATTENDEES LIST |
| 27-MAR-1996 | GENERAL CORRESP To FDA | OTHER | CMC TECHNICAL MEETING AGENDA |
| 27-MAR-1996 | PHONE CALL | OTHER | CMC MEETING ATTENDEES; AGENDA; |
| 29-MAR-1996 | FDA REPORT | ANNUAL RPT | |
| 02-APR-1996 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 03-APR-1996 | AMENDMENT | CLINICAL | STUDY |
| 05-APR-1996 | PHONE CALL | OTHER | MEETING BRIEFING PACKAGE |
| 09-APR-1996 | PHONE CALL | OTHER | MEETING BRIEFING PACKAGE |
| 10-APR-1996 | AMENDMENT | CLINICAL | STUDY |
| 11-APR-1996 | AMENDMENT | CLINICAL | STUDY |
| 12-APR-1996 | PHONE CALL | OTHER | MEETING |

| COMM DATE | COMM TYPE | DESCRIPTION | |
|---|---|---|---|
| 15-APR-1996 | PHONE CALL | OTHER | MEETING |
| 16-APR-1996 | PHONE CALL | OTHER | |
| 18-APR-1996 | PHONE CALL | OTHER | |
| 18-APR-1996 | PHONE CALL | OTHER | SCIENTIFIC ISSUES |
| 22-APR-1996 | PHONE CALL | OTHER | SCIENTIFIC ISSUES |
| 24-APR-1996 | PHONE CALL | OTHER | SCIENTIFIC ISSUES |
| 26-APR-1996 | PHONE CALL | OTHER | SCIENTIFIC ISSUES |
| 03-MAY-1996 | PHONE CALL | OTHER | SCIENTIFIC ISSUES |
| 06-MAY-1996 | PHONE CALL | OTHER | SCIENTIFIC ISSUES |
| 20-MAY-1996 | AMENDMENT | CLINICAL | STUDY |
| 20-MAY-1996 | PHONE CALL | CLINICAL | STUDY |
| 22-MAY-1996 | PHONE CALL | OTHER | LETTER |
| 24-MAY-1996 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 24-MAY-1996 | PHONE CALL | OTHER | LETTER |
| 29-MAY-1996 | PHONE CALL | OTHER | LETTER |
| 29-MAY-1996 | PHONE CALL | CLINICAL | SAFETY REPORT |
| 30-MAY-1996 | PHONE CALL | OTHER | LETTER |
| 03-JUN-1996 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 04-JUN-1996 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 04-JUN-1996 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 07-JUN-1996 | GENERAL CORRESP From FDA | OTHER | FDA RESPONSE TO THE ISSUES |
| 11-JUN-1996 | GENERAL CORRESP From FDA | OTHER | ACKNOWLEDGEMENT OF BRIEFING PACKAGE |
| 19-JUN-1996 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 19-JUN-1996 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 19-JUN-1996 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 20-JUN-1996 | PHONE CALL | OTHER | CLARIFICATIONS |

| COMM DATE | COMM TYPE | DESCRIPTION | |
|---|---|---|---|
| 24-JUN-1996 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 01-JUL-1996 | AMENDMENT | CLINICAL | STUDY |
| 16-JUL-1996 | PHONE CALL | CLINICAL | STUDY |
| 19-JUL-1996 | PHONE CALL | OTHER | FOLLOW UP |
| 02-AUG-1996 | PHONE CALL | OTHER | FOLLOW UP |
| 02-AUG-1996 | PHONE CALL | OTHER | DISCUSSION |
| 28-AUG-1996 | PHONE CALL | OTHER | FOLLOW UP |
| 29-AUG-1996 | PHONE CALL | OTHER | CONTACT PERSON |
| 03-SEP-1996 | PHONE CALL | MICROBIOLOGY | |
| 13-SEP-1996 | AMENDMENT | CLINICAL | STUDY |
| 20-SEP-1996 | PHONE CALL | OTHER | PRE-NDA MEETING AND MICRO REQUEST |
| 01-OCT-1996 | AMENDMENT | OTHER | MEETING REQUEST |
| 01-OCT-1996 | PHONE CALL | OTHER | PRE-NDA MEETING |
| 04-OCT-1996 | PHONE CALL | OTHER | PRE-NDA MEETING |
| 07-OCT-1996 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 08-OCT-1996 | PHONE CALL | OTHER | PRE-NDA MEETING |
| 10-OCT-1996 | PHONE CALL | OTHER | PRE-NDA MEETING |
| 11-OCT-1996 | GENERAL CORRESP From FDA | OTHER | MEETING MINUTES |
| 11-OCT-1996 | GENERAL CORRESP From FDA | OTHER | MEETING MINUTES |
| 15-OCT-1996 | PHONE CALL | OTHER | PRE-NDA MEETING |
| | PHONE CALL | CLINICAL | SAFETY REPORT |
| 16-OCT-1996 | PHONE CALL | OTHER | PRE-NDA MEETING |
| 18-OCT-1996 | PHONE CALL | OTHER | CONFIRMATION |
| 21-OCT-1996 | PHONE CALL | OTHER | PRE-NDA MEETING |
| 22-OCT-1996 | AMENDMENT | OTHER | BRIEFING PACKAGE |
| 23-OCT-1996 | FDA REPORT | CLINICAL | SAFETY REPORT |

| COMM DATE | COMM TYPE | | DESCRIPTION | |
|---|---|---|---|---|
| 23-OCT-1996 | FDA REPORT | | CLINICAL | SAFETY REPORT |
| 23-OCT-1996 | FDA REPORT | | CLINICAL | SAFETY REPORT |
| 23-OCT-1996 | FDA REPORT | | CLINICAL | SAFETY REPORT |
| 24-OCT-1996 | PHONE CALL | | CMC | DRUG PRODUCT |
| 25-OCT-1996 | PHONE CALL | | OTHER | NDA NUMBER ASSIGNMENTS |
| 25-OCT-1996 | PHONE CALL | | OTHER | |
| 28-OCT-1996 | FDA REPORT | | CLINICAL | SAFETY REPORT |
| 01-NOV-1996 | GENERAL CORRESP From FDA | | LABEL | |
| 01-NOV-1996 | PHONE CALL | | OTHER | SCHEDULE |
| 01-NOV-1996 | PHONE CALL | | OTHER | |
| 04-NOV-1996 | AMENDMENT | | CLINICAL | STUDY |
| 05-NOV-1996 | PHONE CALL | | OTHER | DISCUSSION |
| 06-NOV-1996 | GENERAL CORRESP From FDA | | OTHER | FDA FAX |
| 07-NOV-1996 | PHONE CALL | | OTHER | DISCUSS FDA'S EXPECTATIONS |
| 14-NOV-1996 | AMENDMENT | | PRECLINICAL | PHARMACOLOGY |
| 14-NOV-1996 | PHONE CALL | | OTHER | DEMONSTRATION |
| 15-NOV-1996 | MEETING MINUTES | | OTHER | MEETING MINUTES |
| 20-NOV-1996 | PHONE CALL | | OTHER | |
| 20-NOV-1996 | PHONE CALL | | OTHER | SCHEDULING DEMONSTRATION, |
| 26-NOV-1996 | GENERAL CORRESP From FDA | | OTHER | MEETING MINUTES |
| 02-DEC-1996 | AMENDMENT | | CLINICAL | STUDY |
| 12-DEC-1996 | GENERAL CORRESP From FDA | | MICROBIOLOGY | COMMENTS |
| 13-DEC-1996 | PHONE CALL | OTHER | DISCUSSION | |
| 16-DEC-1996 | PHONE CALL | OTHER | | |
| 02-JAN-1997 | AMENDMENT | CLINICAL | STUDY | |
| 07-JAN-1997 | PHONE CALL | | OTHER | SCHEDULING DEMONSTRATION |

| COMM DATE | COMM TYPE | DESCRIPTION | |
|---|---|---|---|
| 13-JAN-1997 | PHONE CALL | OTHER | LOGISTICS |
| 14-JAN-1997 | PHONE CALL | OTHER | LOGISTICS |
| 21-JAN-1997 | PHONE CALL | OTHER | SCHEDULING CONVERSATIONS |
| 23-JAN-1997 | MEETING MINUTES | OTHER | MINUTES OF MEETING |
| 23-JAN-1997 | PHONE CALL | CLINICAL | STUDY |
| 24-JAN-1997 | AMENDMENT | CLINICAL | SUMMARY |
| | AMENDMENT | CLINICAL | SUMMARY |
| | AMENDMENT | CLINICAL | SUMMARY |
| 27-JAN-1997 | AMENDMENT | CLINICAL | STUDY |
| 27-JAN-1997 | MEETING MINUTES | OTHER | MINUTES DEMONSTRATION |
| 27-JAN-1997 | PHONE CALL | CLINICAL | STUDY |
| 29-JAN-1997 | PHONE CALL | CLINICAL | SAFETY REPORT |
| 30-JAN-1997 | PHONE CALL | OTHER | PROVIDIDNG ELECTRONIC FILES |
| 03-FEB-1997 | AMENDMENT | CLINICAL | STUDY |
| 05-FEB-1997 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 07-FEB-1997 | PHONE CALL | CLINICAL | STUDY |
| 18-FEB-1997 | PHONE CALL | OTHER | |
| 19-FEB-1997 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 26-FEB-1997 | AMENDMENT | CLINICAL | STUDY |
| 19-MAR-1997 | AMENDMENT | CLINICAL | STUDY |
| 02-APR-1997 | FDA REPORT | ANNUAL RPT | |
| 10-APR-1997 | PHONE CALL | OTHER | |
| 11-APR-1997 | PHONE CALL | CLINICAL | STUDY |
| 11-APR-1997 | PHONE CALL | OTHER | RESPONSE |
| 14-APR-1997 | PHONE CALL | OTHER | RESPONSE |
| 16-APR-1997 | PHONE CALL | OTHER | RESPONSE |

| COMM DATE | COMM TYPE | DESCRIPTION | |
|---|---|---|---|
| 18-APR-1997 | PHONE CALL | OTHER | RESPONSE |
| 21-APR-1997 | AMENDMENT | CLINICAL | STUDY |
| 21-APR-1997 | PHONE CALL | OTHER | RESPONSE |
| 22-APR-1997 | PHONE CALL | OTHER | RESPONSE |
| 28-APR-1997 | PHONE CALL | OTHER | RESPONSE |
| 01-MAY-1997 | PHONE CALL | OTHER | |
| 14-MAY-1997 | PHONE CALL | OTHER | QUESTIONS |
| 15-MAY-1997 | PHONE CALL | OTHER | QUESTIONS |
| 16-MAY-1997 | AMENDMENT | CLINICAL | STUDY |
| 16-MAY-1997 | GENERAL CORRESP To FDA | CLINICAL | STUDY |
| 16-MAY-1997 | PHONE CALL | OTHER | QUESTIONS |
| 21-MAY-1997 | PHONE CALL | CMC | DRUG PRODUCT |
| 23-MAY-1997 | PHONE CALL | CMC | DRUG PRODUCT |
| 30-MAY-1997 | PHONE CALL | CLINICAL | STUDY |
| 02-JUN-1997 | AMENDMENT | CLINICAL | STUDY |
| 03-JUN-1997 | PHONE CALL | OTHER | SCHEDULING OF TELECONFERENCE |
| 10-JUN-1997 | PHONE CALL | CLINICAL | STUDY |
| 30-JUN-1997 | PHONE CALL | OTHER | CONFIRM NDA APPROACH |
| 08-JUL-1997 | AMENDMENT | CLINICAL | STUDY |
| 09-JUL-1997 | AMENDMENT | CLINICAL | STUDY |
| 25-JUL-1997 | AMENDMENT | CLINICAL | STUDY |
| 25-JUL-1997 | PHONE CALL | OTHER | |
| 04-AUG-1997 | GENERAL CORRESP To FDA | OTHER | BRIEFING DOCUMENT |
| 04-AUG-1997 | PHONE CALL | CLINICAL | STUDY |
| 05-AUG-1997 | GENERAL CORRESP To FDA | CLINICAL | |
| 06-AUG-1997 | FDA REPORT | CLINICAL | SAFETY REPORT |

| COMM DATE | COMM TYPE | DESCRIPTION | |
|---|---|---|---|
| 06-AUG-1997 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 06-AUG-1997 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 13-AUG-1997 | PHONE CALL | OTHER | PROVIDING ELECTRONIC FILES |
| 13-AUG-1997 | PHONE CALL | OTHER | ELECTRONIC DELIVERIES. |
| 13-AUG-1997 | PHONE CALL | OTHER | |
| 13-AUG-1997 | PHONE CALL | OTHER | |
| 14-AUG-1997 | PHONE CALL | CLINICAL | STUDY |
| 15-AUG-1997 | PHONE CALL | OTHER | PROVIDING ELECTRONIC FILES |
| 20-AUG-1997 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 02-SEP-1997 | PHONE CALL | OTHER | ELECTRONIC DELIVERIES |
| 25-SEP-1997 | PHONE CALL | CLINICAL | STUDY |
| 16-OCT-1997 | PHONE CALL | CLINICAL | SAFETY REPORT |
| 17-OCT-1997 | AMENDMENT | CLINICAL | STUDY |
| 29-OCT-1997 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 04-NOV-1997 | PHONE CALL | CLINICAL | SAFETY REPORT |
| 05-NOV-1997 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 19-NOV-1997 | AMENDMENT | CLINICAL | STUDY |
| 25-NOV-1997 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 12-DEC-1997 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 25-FEB-1998 | AMENDMENT | CLINICAL | STUDY |
| 20-MAR-1998 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 20-APR-1998 | FDA REPORT | ANNUAL RPT | |
| 20-APR-1998 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 03-JUN-1998 | AMENDMENT | CLINICAL | STUDY |
| 16-JUN-1998 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 17-JUN-1998 | FDA REPORT | CLINICAL | SAFETY REPORT |

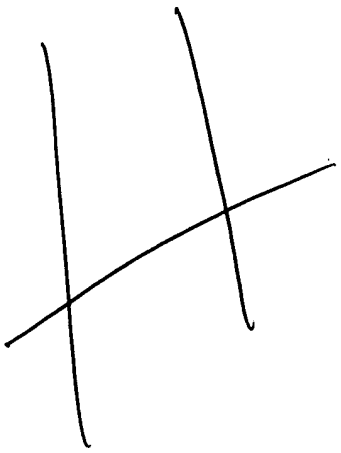
| COMM DATE | COMM TYPE | DESCRIPTION | |
|---|---|---|---|
| 17-JUN-1998 | GENERAL CORRESP To FDA | CLINICAL | STUDY |
| | GENERAL CORRESP To FDA | CLINICAL | STUDY |
| 22-JUN-1998 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 22-JUN-1998 | PHONE CALL | OTHER | MISCELLANEOUS QUESTIONS |
| 29-JUN-1998 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 01-JUL-1998 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 02-JUL-1998 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 06-JUL-1998 | AMENDMENT | CLINICAL | STUDY |
| 10-JUL-1998 | FDA REPORT | CLINICAL | SAFETY |
| 10-JUL-1998 | FDA REPORT | CLINICAL | SAFETY |
| 10-JUL-1998 | GENERAL CORRESP To FDA | CLINICAL | STUDY |
| | GENERAL CORRESP To FDA | CLINICAL | STUDY |
| 24-JUL-1998 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 27-JUL-1998 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 28-JUL-1998 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 30-JUL-1998 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 31-JUL-1998 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 07-AUG-1998 | PHONE CALL | OTHER | DISCUSSION |
| 10-AUG-1998 | GENERAL CORRESP To FDA | OTHER | |
| 14-AUG-1998 | GENERAL CORRESP To FDA | OTHER | |
| 18-AUG-1998 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 18-AUG-1998 | FDA REPORT | CLINICAL | SAFETY |
| 24-AUG-1998 | AMENDMENT | CLINICAL | STUDY |
| 03-SEP-1998 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 28-SEP-1998 | AMENDMENT | CLINICAL | STUDY |
| 01-OCT-1998 | AMENDMENT | CLINICAL | STUDY |

| COMM DATE | COMM TYPE | DESCRIPTION | |
|---|---|---|---|
| 01-OCT-1998 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 02-OCT-1998 | GENERAL CORRESP To FDA | CLINICAL | STUDY |
| 12-OCT-1998 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 13-OCT-1999 | PHONE CALL | CLINICAL | STUDY |
| 16-OCT-1998 | GENERAL CORRESP To FDA | CLINICAL | STUDY |
| | GENERAL CORRESP To FDA | CLINICAL | STUDY |
| 20-OCT-1998 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 23-OCT-1998 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 26-OCT-1998 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 28-OCT-1998 | FDA REPORT | CLINICAL | SAFETY |
| 04-NOV-1998 | GENERAL CORRESP | CLINICAL | STUDY |
| 11-NOV-1998 | AMENDMENT | CLINICAL | STUDY |
| 23-NOV-1998 | AMENDMENT | CLINICAL | STUDY |
| 02-DEC-1998 | AMENDMENT | CLINICAL | STUDY |
| 04-DEC-1998 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 29-DEC-1998 | AMENDMENT | CLINICAL | STUDY |
| 13-JAN-1999 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 25-JAN-1999 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 27-JAN-1999 | AMENDMENT | CLINICAL | STUDY |
| 27-JAN-1999 | GENERAL CORRESP To FDA | CLINICAL | STUDY |
| 29-JAN-1999 | PHONE CALL | CLINICAL | SAFETY REPORT |
| 01-FEB-1999 | AMENDMENT | CLINICAL | STUDY |
| 01-FEB-1999 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 02-FEB-1999 | AMENDMENT | CLINICAL | STUDY |
| | AMENDMENT | CLINICAL | CRF |
| 02-FEB-1999 | FDA REPORT | CLINICAL | SAFETY REPORT |

| COMM DATE | COMM TYPE | DESCRIPTION | |
|---|---|---|---|
| 11-FEB-1999 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 19-FEB-1999 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 22-FEB-1999 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 04-MAR-1999 | AMENDMENT | CLINICAL | STUDY |
| 04-MAR-1999 | AMENDMENT | CLINICAL | STUDY |
| 09-MAR-1999 | AMENDMENT | CLINICAL | STUDY |
| 09-MAR-1999 | AMENDMENT | CLINICAL | STUDY |
| 09-MAR-1999 | PHONE CALL | CMC | DRUG PRODUCT |
| 10-MAR-1999 | AMENDMENT | CLINICAL | STUDY |
| 23-MAR-1999 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 24-MAR-1999 | FDA REPORT | ANNUAL RPT | |
| 29-MAR-1999 | PHONE CALL | LABEL | |
| 05-APR-1999 | AMENDMENT | CLINICAL | STUDY |
| 07-APR-1999 | PHONE CALL | LABEL | |
| 13-APR-1999 | PHONE CALL | LABEL | |
| 13-APR-1999 | PHONE CALL | LABEL | |
| 23-APR-1999 | AMENDMENT | CLINICAL | STUDY |
| 28-APR-1999 | PHONE CALL | CLINICAL | STUDY |
| 07-MAY-1999 | AMENDMENT | CLINICAL | STUDY |
| 10-MAY-1999 | PHONE CALL | LABEL | |
| 13-MAY-1999 | PHONE CALL | CLINICAL | STUDY |
| 20-MAY-1999 | AMENDMENT | CLINICAL | STUDY |
| | AMENDMENT | CLINICAL | STUDY |
| 20-MAY-1999 | PHONE CALL | OTHER | NUMEROUS ISSUES |
| 26-MAY-1999 | PHONE CALL | OTHER | NUMEROUS ISSUES |
| 02-JUN-1999 | PHONE CALL | LABEL | |

| COMM DATE | COMM TYPE | DESCRIPTION | |
|---|---|---|---|
| 07-JUN-1999 | AMENDMENT | CLINICAL | PROTOCOL AMENDMENT |
| 07-JUN-1999 | MEETING MINUTES | CLINICAL | STUDY |
| 07-JUN-1999 | PHONE CALL | OTHER | NUMEROUS ISSUES |
| 10-JUN-1999 | PHONE CALL | OTHER | NUMEROUS ISSUES |
| 17-JUN-1999 | PHONE CALL | CLINICAL | NUMEROUS ISSUES |
| 21-JUN-1999 | AMENDMENT | CLINICAL | STUDY |
| 23-JUN-1999 | AMENDMENT | CLINICAL | STUDY |
| | AMENDMENT | CLINICAL | STUDY |
| | AMENDMENT | CLINICAL | STUDY |
| | AMENDMENT | CLINICAL | STUDY |
| | AMENDMENT | CLINICAL | STUDY |
| 24-JUN-1999 | MEETING MINUTES | CLINICAL | STUDY |
| 24-JUN-1999 | PHONE CALL | OTHER | NUMEROUS ISSUES |
| 01-JUL-1999 | GENERAL CORRESP To FDA | CLINICAL | STUDY |
| 01-JUL-1999 | PHONE CALL | OTHER | NUMEROUS ISSUES |
| 06-JUL-1999 | MEETING MINUTES | CLINICAL | STUDY |
| 07-JUL-1999 | AMENDMENT | CLINICAL | STUDY |
| 07-JUL-1999 | AMENDMENT | CLINICAL | STUDY |
| 07-JUL-1999 | PHONE CALL | OTHER | NUMEROUS ISSUES |
| 08-JUL-1999 | AMENDMENT | CLINICAL | STUDY |
| 13-JUL-1999 | AMENDMENT | CLINICAL | STUDY |
| | AMENDMENT | CLINICAL | STUDY |
| 15-JUL-1999 | | OTHER | NUMEROUS ISSUES |
| 21-JUL-1999 | AMENDMENT | CLINICAL | STUDY |
| | AMENDMENT | CLINICAL | STUDY |
| 22-JUL-1999 | PHONE CALL | CMC | DRUG PRODUCT |

| COMM DATE | COMM TYPE | DESCRIPTION | |
|---|---|---|---|
| 22-JUL-1999 | PHONE CALL | OTHER | |
| 22-JUL-1999 | PHONE CALL | CLINICAL | STUDY |
| 26-JUL-1999 | AMENDMENT | CLINICAL | STUDY |
| 26-JUL-1999 | PHONE CALL | CMC | DRUG PRODUCT |
| 04-AUG-1999 | AMENDMENT | CLINICAL | STUDY |
| 04-AUG-1999 | PHONE CALL | OTHER | RESPONSE TO FDA VOICE MAIL |
| 06-AUG-1999 | AMENDMENT | CLINICAL | STUDY |
| 06-AUG-1999 | AMENDMENT | CLINICAL | STUDY |
| 09-AUG-1999 | GENERAL CORRESP From FDA | CLINICAL | STUDY |
| 09-AUG-1999 | PHONE CALL | OTHER | |
| 17-AUG-1999 | AMENDMENT | CLINICAL | STUDY |
| 20-AUG-1999 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 30-AUG-1999 | AMENDMENT | CMC | DRUG PRODUCT |
| 30-AUG-1999 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 30-AUG-1999 | GENERAL CORRESP To FDA | CLINICAL | STUDY |
| 31-AUG-1999 | PHONE CALL | CMC | DRUG PRODUCT |
| 08-SEP-1999 | AMENDMENT | CLINICAL | STUDY |
| 13-SEP-1999 | FDA REPORT | CLINICAL | SAFETY REPORT |
| 14-SEP-1999 | AMENDMENT | CLINICAL | STUDY |
| 16-SEP-1999 | AMENDMENT | CLINICAL | STUDY |
| | AMENDMENT | CLINICAL | STUDY |
| | AMENDMENT | CLINICAL | STUDY |
| | AMENDMENT | CLINICAL | STUDY |
| 21-SEP-1999 | FDA REPORT | CLINICAL | SAFETY REPORT |



PATENT
Atty. Docket No.: 3804.0055

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No. 4,668,669 )
)
Issued: May 26, 1987 )
)
To: Jean-Claude Barriere, Claude Cotrel, )
Jean-Marc Paris )
)
Assignee: Rhone-Poulenc Rorer S.A. )
)
For: PRISTINAMYCIN $II_B$ DERIVATIVES )
AND COMPOSITIONS CONTAINING )
THEM )

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

**CERTIFICATION**

I, CHARLES E. VAN HORN, do hereby certify that this accompanying application for extension of the term of U.S. Patent 4,668,669 under 35 U.S.C. § 156 including its attachments and supporting papers is being submitted as one original and four (4) copies thereof.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

By: Charles E. Van Horn
Charles E. Van Horn
Reg. No. 40,266

Date: November 10, 1999

LAW OFFICES
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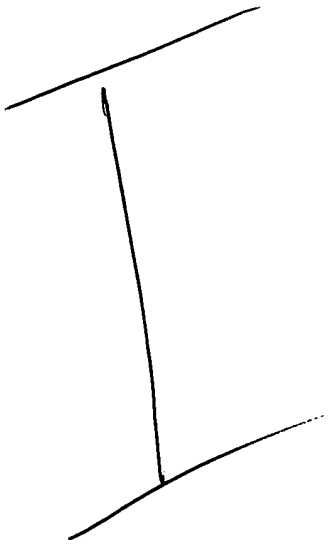
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
SHINGTON, D. C. 20005
202-408-4000



PATENT
Atty. Docket No.: 3804.0055

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No. 4,668.669 )
)
Issued: May 26, 1987 )
)
To: Jean-Claude Barriere, Claude Cotrel, )
Jean-Marc Paris )
)
Assignee: Rhone-Poulenc Rorer S.A. )
)
For: PRISTINAMYCIN $II_B$ DERIVATIVES )
AND COMPOSITIONS CONTAINING )
THEM )

**ATTN: BOX PATENT EXTENSION**
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

**DECLARATION ACCOMPANYING APPLICATION UNDER 35 U.S.C. § 156 FOR EXTENSION OF PATENT TERM**

I, CHARLES E. VAN HORN, do hereby declare:

I am a patent attorney authorized to practice before the United States Patent and Trademark Office and I have been appointed as an attorney by the Patent Assignee, Rhone-Poulenc Rorer S.A., with regard to this application for extension of the term of U.S. Patent 4,668,669 and to transact all business in the U.S. Patent and Trademark Office in connection therewith.

I have reviewed and understand the contents of the accompanying application being submitted pursuant to 37 C.F.R. § 1.740.

I believe that the patent is subject to extension pursuant to 37 C.F.R. § 1.710.

LAW OFFICES
NNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
SHINGTON, D. C. 20005
202-408-4000

I believe an extension of the length claimed is justified under 35 U.S.C. § 156 and applicable regulations.

I believe the patent for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 C.F.R. § 1.720.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

By: Charles E. Van Horn

Charles E. Van Horn
Reg. No. 40,266

Date: November 10, 1999

LAW OFFICES
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& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, D. C. 20005
202-408-4000